The Global Burden Attributable to Low Bone Mineral Density

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El Dr. Joan Miquel Nolla Solé, Professor Agregat del Departament de Ciències Clíniques de la Universitat de Barcelona i la Dra Lyn March, Professor at Northern Medical School at the University of Sydney

CERTIFIQUEN

Que la Tesi Doctoral **"THE GLOBAL BURDEN ATTRIBUTABLE TO LOW BONE MINERAL DENSITY"**, presentada per Lídia Sànchez Riera, ha estat realitzada sota la seva direcció i reuneix les característiques metodològiques necessàries per ser defensada davant del tribunal corresponent.

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To Philip Sambrook and Jian Sheng (Charles) Chen

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acknowledgement of the many
steps you took towards the
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CONTENTS:

LA CÀRREGA EN SALUT MUNDIAL ATRIBUÏBLE A LA BAIXA DENSITAT MINERAL ÒSSIA (*THE GLOBAL BURDEN ATTRIBUTABLE TO LOW BONE MINERAL DENSITY*)

Resum en català de la memòria presentada per Lídia Sànchez Riera per optar al títol de Doctor en Medicina

Nota: Referències bibliogràfiques, taules, figures, apèndixs, llista d'abreviacions i produccions científiques relacionades amb aquesta memòria es trobaran formant part de la tesi original en anglès en el seu ordre i numeració originals).

Índex

1 Introducció

1.1 Osteoporosi i fractures osteoporòtiques

L'osteoporosi es defineix com una malaltia sistèmica del sistema esquelètic caracteritzada per una baixa massa òssia i un deteriorament de la microarquitectura de l'òs, amb el conseqüent augment de la fragilitat òssia i de la susceptibilitat a fractura (NIH Consensus Development Panel on Osteoporosis Prevention 2001). Es comporta com una malaltia silent; un alt percentatge de la gent afectada ignoren que pateixen la condició. Com a resultat, les conseqüències de l'osteoporosi són millor estudiades quan es mesura l'impacte de la seva conseqüència clínica, les fractures osteoporòtiques (també conegudes com "fractures per fragilitat), les quals acostumen a tenir lloc després d'un traumatisme de baix impacte, com per exemple, una caiguda casual. Les localitzacions més habituals i millor caracteritzades són, per ordre del seu impacte ens salut, maluc, vèrtebra, i canell. Existeixen altres fractures en localitzacions perifèriques considerades com osteoporòtiques, com húmer proximal, pelvis, costella, tíbia proximal, clavícula, mà i peu (Seeley, Browner et al. 1991).

Durant les dues darreres dècades, la definició operativa d' *osteoporosi* s'ha basat en els valors de densitat mineral òssia (DMO, o *BMD* de l'anglès *bone mineral density*): en dones postmenopàusiques i en homes a partir de 50 anys d'edat, el diagnòstic d'osteoporosi es realitza quan la DMO mesurada per DXA (*dual-energy-X-ray*

absorptiometry o *dual-X-ray absorptiometry*) a columna lumbar, maluc total o coll femoral (en ocasions el terç distal de radi també es pot utilitzar) es troba a -2.5 desviacions estàndard (DE, o SD de l'anglès *standard deviati*on) o per sota de la mitja del valor de DMO en dones joves (*T score* ≤ -2.5) (WHO 1994; Kanis 2008) (Figure 1.1). En dones premenopàusiques i en homes més joves de 50 anys, el diagnòstic es defineix per factors de risc clínic (fractura o altres factors de risc) en presència d' una massa òssia inferior al rang esperat pel gènere i el grup d'edat (*Z score* ≤ -2.0) (Binkley, Bilezikian et al. 2006; Watts, Leslie et al. 2013). En aquesta subpoblació, l'osteoporosi és menys comú, i el cribratge de causes subjacents relacionades amb la seva aparició cal que sigui exhaustiu, donat l'alta freqüència de causes secundàries d'osteoporosi (Khosla, Lufkin et al. 1994).

Malgrat el consens en les definicions anteriors pel diagnòstic d'osteoporosi i l'evidència existent del paper de la DMO en el risc de fractura, la sensibilitat de la DMO per predir una fractura és limitada, i el seu valor predictiu millora quan els factors clínics es tenen en compte. Des d'un punt de vista epidemiològic, mesures com la probabilitat de fractura a 10 anys es consideren més adequades per definir el risc de fractura, l'autèntica càrrega en salut de l'osteoporosi (Genant, Cooper et al. 1999; Kanis and Gluer 2000).

1.2 Impacte en salut de les fractures osteoporòtiques

Els resultats derivats de les fractures osteoporòtiques poden anar des del dolor crònic, la pèrdua de mobilitat i la independència, fins a la institucionalització i la mort

(Johnell and Kanis 2004; Johnell and Kanis 2006; Bliuc, Nguyen et al. 2009; Bertram, Norman et al. 2011).

La fractura de maluc constitueix el tipus de fractura osteoporòtica amb les pitjors conseqüències per la salut, en part perquè el seu pic d'incidència, clàssicament, succeeix en població d'edat avançada, entre el 70 i els 79 anys d'edat (Johnell and Kanis 2004). Dins de l'any posterior a una fractura de maluc, la mortalitat acumulada arriba fins el 37% en homes i el 25% en dones, i és considerablement més elevada que en la població general de la mateixa edat (Kanis, Oden et al. 2003; Kannegaard, van der Mark et al. 2010). Aproximadament la meitat d'individus perden el seu nivell de funció física habitual, i molts requereixen assistència a llarg termini (Magaziner, Simonsick et al. 1990; Sernbo and Johnell 1993; Melton 2003).

Les fractures vertebrals són les segones en ordre d'impacte en salut. Poden causar dolor i limitació del moviment espinal i afecten considerablement la qualitat de vida (Naves Diaz, Diaz Lopez et al. 2001). La seva incidència i prevalença augmenten de forma constant des dels 50 fins al 80 anys d'edat (O'Neill, Felsenberg et al. 1996; Jansson, Blomqvist et al. 2010). Una cinquena part dels afectats requereix hospitalització, i en ocasions, assistència a llarg termini (Silverman 1992; Ross 1997). Aproximadament només un terç dels col·lapses vertebrals osteoporòtics provoquen dolor agut, (Cooper, Atkinson et al. 1992), però també són causa de discapacitat (Silverman 1992; Ross 1997). Conseqüències a llarg termini com la cifosi, la malaltia pulmonar restrictiva i l'estenosi espinal contribueixen igualment a la pèrdua de qualitat de vida i a la mortalitat (Kado, Browner et al. 1999), la qual es troba clarament augmentada respecte la població general i és proporcional al

número de fractures prevalents (Kado, Browner et al. 1999; Kanis, Oden et al. 2004).

Les fractures de canell tendeixen a ocórrer en edats més precoces, amb un pic d'incidència entre els 40 i els 65 anys. Al voltant d'una cinquena part de les fractures de Colles (fractures del radi distal amb desplaçament dorsal del radi, amb o sense fractura de cúbit) en països desenvolupats resulten en hospitalització (O'Neill, Cooper et al. 2001). Nomes un 50% dels afectats refereix una bona recuperació funcional als 6 mesos (Kaukonen, Karaharju et al. 1988).

La mortalitat prematura després d'una fractura persisteix significativament més elevada que en la població general no només durant el primer any post-fractura, sinó també fins a un període de 5-15 anys, depenent del grup d'edat i la localització de la fractura (Bliuc, Nguyen et al. 2009; Melton, Achenbach et al. 2013).

1.3 Epidemiologia de l'osteoporosi i de les fractures osteoporòtiques

En una revisió molt recent, la prevalença de l'osteoporosi en quatre cinquenes parts de la població mundial s'ha estimat en un 3% en homes i un 10% en dones de 50 a 59 anys (Oden, McCloskey et al. 2013). Aquest percentatge incrementa al 6% i al 19%, respectivament, en poblacions entre els 60 i els 69 anys, seguit d'una prevalença del 9% i del 35%, respectivament, en aquells amb edat compreses entre els 70 i els 79 anys, i finalment, del 19% i del 51%, respectivament, en població a partir dels 80 anys d'edat. Els autors han calculat que al voltant de 2,7 milions de

fractures de maluc van tenir lloc en el 2010 a la població mundial, de les quals la meitat eren atribuïbles a osteoporosi (264.000 en homes i 1,10 milions en dones), i per tant, evitables.

Treballs previs en la iniciativa *the global burden of diseases* (GBD, en català la "càrrega mundial de les malalties") han estimat que un total de 9 milions de fractures osteoporòtiques van tenir lloc en el món durant el 2000, de les quals 1,6 milions eren de maluc (70% dones), 1,7 milions eren de canell (80% dones) i 1,4 milions eren fractures vertebral clíniques (58% dones) (Johnell and Kanis 2006). Malgrat que les fractures de maluc representaven solament un 18,2% de totes les fractures, constituïen un 40% de tot l'impacte en salut mundial degut a fractures. El nombre més gran de fractures succeí a Europa, seguit del Pacífic occidental, el sud-est d' Àsia i les Amèriques, contribuint col·lectivament al 97% de totes les fractures al món, subratllant la influència del creixement de la població amb edat avançada. En combinar mortalitat i morbiditat en una mateixa mesura estàndard coneguda com DALYs (de l'angles *disability-adjusted life years*), les fractures osteropòtiques eren causa de més DALYs perduts en comparació amb l'artritis reumatoide i tots els tipus de càncer, amb excepció del càncer de pulmó (Johnell and Kanis 2006).

Considerant l'envelliment progressiu de la població mundial, s'ha projectat un augment del 300% en la incidència mundial de fractura de maluc el 2050 comparat amb el 1990 (Gullberg, Johnell et al. 1997).

Un aspecte important en l'epidemiologia de les fractures osteoporòtiques és que la incidència de fractura és país-depenent (Kanis, Johnell et al. 2002; Roy, Pye et al.

2002) (Table 1.1), així com també ho són els nivells poblacionals de DMO (Sanchez-Riera, Wilson et al. 2010). Aquesta variabilitat va més enllà de les diferències en l'expectativa de vida i la proporció de població senil, i probablement reflecteixen el paper de múltiples factors genètics, culturals i mediambientals.

1.4 Cost econòmic de les fractures osteoporòtiques

El cost econòmic de l'osteoporosi i de les fractures osteoporòtiques prové de les conseqüències a curt termini (hospitalització i cirurgia, per exemple), i de les conseqüències a llarg termini, com la incapacitat crònica, les intervencions farmacològiques i la institucionalització.

A la Unió Europea, el cost de l'osteoporosi el 2010 es va calcular en 37.000 milions d'euros, dels quals, un 66 % corresponien al tractament de fractures agudes, un 5% al tractament farmacològic, i el 29% restant a l'assistència sòcio-sanitària a llarg termini. La meitat d'aquests costos eren resultat de fractures de maluc. Els costos derivats de les fractures per fragilitat superaven altres condicions amb gran potencial de discapacitat, com els accidents cerebrovasculars, el Parkinson i l'artritis reumatoide (Hernlund, Svedbom et al. 2013; Strom, Borgstrom et al. 2013).

Degut als canvis demogràfics de la població, els costos derivats de les fractures osteoporòtiques a Europa augmentaran en un 22% del 2010 al 2025 (Hernlund, Svedbom et al. 2013). Aquest increment en la incidència de les fractures i el conseqüent cost també s'ha predit per Nord-Amèrica, Llatino-Amèrica, Australàsia, Orient Mitjà, Nord-Àfrica i Àsia (Cooper, Campion et al. 1992; Gullberg, Johnell et al.

1997). De fet, l' increment progressiu de l'esperança de vida i de la població general a Àsia i Llatino-Amèrica està provocant un viratge de l'impacte de l'osteoporosi cap a aquestes regions del món. Pels volts del 2050, es calcula que la meitat de les fractures de maluc tindran lloc a Àsia (Cooper, Campion et al. 1992).

1.5 Factors de risc d'osteoporosi i fractura osteoporòtica. Paper de la densitat mineral òssia i dels factors de risc clínic

La resistència òssia reflecteix principalment la integració entre DMO i qualitat òssia. La darrera pot esdevenir complicada de mesurar de forma generalitzada a la pràctica clínica, sobretot des d'un punt de vista poblacional. La DMO, d'altra banda, és un factor de risc de fractura ben definit (Marshall, Johnell et al. 1996; Johnell, Kanis et al. 2005), i pot ser mesurada amb tècniques estandarditzades que són objectives, reproduïbles, no invasives, ràpides i relativament econòmiques. A més a més, el potencial modificador d'una gran varietat de mesures farmacològiques i no farmacològiques sobre la DMO es troba ben caracteritzat. Per tant, la DMO ofereix un escenari excel·lent pel maneig i el seguiment dels individus amb alt risc de fractura.

L' ús de la DXA central (columna i maluc) roman com la tècnica per mesurar DMO més àmpliament utilitzada i validada, i és el mètode d'elecció segons les recomanacions dels organismes internacionals experts (WHO 1994; 2007). Tot i l'existència d'un llindar establert pel diagnòstic d'osteoporosi amb l'ús de DXA (T score ≤ -2.5), el risc de fractura degut a una baixa DMO és continu més que no pas categòric, i de fet, la major part de les fractures osteoporòtiques succeeixen en

individus amb osteopènia (es a dir, amb T scores entre -1 i -2.5) (Siris, Chen et al. 2004). Per tant, la definició d'osteoporosi amb DXA, d'alguna manera arbitrària, té una baixa sensibilitat per detectar individus amb alt risc de fractura.

L'anomenat gradient de risc de fractura (en anglès, *gradient of risk*, GR) s'ha definit com el risc relatiu (*relative risk*, RR) de fractura per cada unitat de DMO disminuïda. Una important metanàlisi del 1996 (Marshall, Johnell et al. 1996) va trobar que les mesures de DMO a maluc, columna lumbar i canell podien predir conjuntament l'esdeveniment d'una fractura amb un GR d'aproximadament 1,5 per cada disminució en una DE de la DMO. El valor del RR millorava quan les mesures eren específiques per cada localització, de manera que la precisió predictiva de la fractura de maluc, per exemple, millorava amb mesures de la DMO realitzades a maluc (Table 1.2), amb un GR de 2,6. Això volia dir que un individu amb un T score de −3 DE a maluc tindria una probabilitat de fractura de 2.6^3 (o aproximadament 17 vegades més) que un altre individu amb un T score de 0 DE. Gairebé 10 anys més tard, una nova metanàlisi basada en 12 cohorts poblacionals prospectives d'Europa occidental, Estats Units, Canadà, Japó i Austràlia, va trobar resultats similars (Johnell, Kanis et al. 2005). En aquest darrer estudi, es va trobar que la DMO a coll femoral (en anglès *femoral neck bone mineral density*, FNBMD) posseïa un bon valor predictiu per fractura de maluc, per qualsevol fractura osteoporòtica, i per qualsevol fractura en general. Tot que l'esdeveniment d'una fractura tenia lloc més sovint en dones, el GR per cada unitat de FNBMD era equivalent entre els dos gèneres, la qual cosa significa que l'excés de risc degut solament a la DMO era comparable entre dones i homes.

El valor predictiu de la DMO per calcular el risc de fractura pot millorar molt amb la incorporació de factors independents de risc clínic (Kanis, Oden et al. 2007). El *Fracture Risk Assessment Tool* (FRAX®), és una iniciativa promoguda per l'Organització Mundial de la Salut (OMS, i en anglès, *World Health Organization*, WHO) i validada per diversos països (http://www.shef.ac.uk/FRAX). Aquesta eina de predicció de fractura és un algoritme dinàmic que integra el GR de FNBMD derivat de la metanàlisi de Johnell i Kanis (Johnell, Kanis et al. 2005) amb 12 factors de risc clínic (Table 1.3), i permet el càlcul d'una probabilitat a 10 anys per fractures de maluc i per qualsevol fractura osteoporòtica, fins i tot en absència de informació de la DMO. Existeixen altres algoritmes per la predicció de fractures, tot i que la seva validació i acceptació per part de la comunitat científica internacional encara esta lluny del FRAX®.

El factor de risc clínic més rellevant per sofrir una fractura és clarament l'edat (Kanis, Johnell et al. 2001), seguit del gènere femení (Johnell and Kanis 2006; Oden, McCloskey et al. 2013), i la història de fractura prèvia (Kanis, Johnell et al. 2004). El paper del pes i l'índex de massa corporal (en anglès *body mass index*, BMI) també es troba ben caracteritzat tant en homes com en dones en diverses parts del món (Cauley, Fullman et al. 2005; De Laet, Kanis et al. 2005; Kaptoge, Reid et al. 2007; Beck, Petit et al. 2009; Kim, Oh et al. 2009; Orito, Kuroda et al. 2009; Genaro, Pereira et al. 2010; Langsetmo, Poliquin et al. 2010; Sheng, Xu et al. 2010). Pel que fa a l'activitat física, la seva influència sobre el risc de fractura és doble: d'una banda, augmenta la qualitat i quantitat d'òs trabecular i cortical, i per tant millora la resistència òssia (Cousins, Petit et al. 2010; Janz, Letuchy et al. 2014); d'una altra banda, l'exercici pot tenir un efecte positiu en la força muscular, l'equilibri i la marxa,

tots components importants en el risc de caigudes en la gent gran (Nevitt, Cummings et al. 1991; Ensrud, Ewing et al. 2007; Wilson, Hilmer et al. 2011; Cauley, Harrison et al. 2013), les quals són un dels factors de risc més important de fractura a la pràctica clínica (Roy, Pye et al. 2002; Ensrud, Ewing et al. 2007; Deprey 2009). Cal tenir en compte que aquesta és una de les limitacions més importants de l'eina FRAX®, la qual, de moment, no incorpora la probabilitat de caiguda en l'algoritme.

Altres factors de risc de fractura inclouen el tabaquisme, l'alcohol i diverses condicions clíniques que s'han identificat com factors independents de baixa DMO i de fractura (Table 1.3, Table 1.4) (Kanis, Borgstrom et al. 2005; Kanis 2008; Kanis, Johansson et al. 2009). Entre les múltiples causes farmacològiques, el tractament corticoideu és clarament el factor de més pes, pel seu gran impacte i prevalença, constituint sovint la primera causa d'osteroporosi secundària en països desenvolupats (Allport 2008; Civitelli and Ziambaras 2008). La deficiència en vitamin D provoca hiperparatiroïdisme secundari i també s'ha associat a l'aparició d'osteoporosi (Holick 2007), i fractures (LeBoff, Kohlmeier et al. 1999; Bischoff-Ferrari, Can et al. 2008; Cauley, Parimi et al. 2009; Nakamura, Saito et al. 2010). Pel que fa als suplements de calci, una de les recomanacions clàssiques generals en el maneig de l'osteoporosi, l'evidència científica recent mostra que la seva influència en la DMO i el risc de fractura és força mínima (Shea, Wells et al. 2004) . No obstant, les guies de maneig clínic recomanen en general complir amb els requeriments diaris de calci, específics per cada període de la vida, preferentment a través de la dieta.

Finalment, diferents ètnies presenten divergències en els nivells poblacionals de DMO (clàssicament, per exemple, la raça negra presenta nivells de DMO més elevats que caucàsics o asiàtics) (Nam, Shin et al. 2010; Yang, Lu et al. 2013) i en l'estructura òssia (relacionades, per exemple, amb diferents paràmetres geomètrics del coll femoral) (Faulkner, Cummings et al. 1993; Pulkkinen, Partanen et al. 2004; Gnudi, Sitta et al. 2007) que igualment influencien en el risc de fractura. És important remarcar que tot i aquestes diferències, el GR de fractura per unitat de DMO a coll femoral (FNBMD) és comparable entre diferent races (Broussard and Magnus 2004; Looker, Melton et al. 2009). Així mateix, l'existència de gens determinants en l'estructura i densitat òssies s'ha demostrat en estudis amb bessons (Slemenda, Christian et al. 1991; Arden and Spector 1997; Harris, Nguyen et al. 1998), i pel fet que la història paterna o materna de fractura de maluc familiar ha demostrat ser un factor de risc consolidat de fractura (Kanis, Johansson et al. 2004).

1.6 Diagnòstic i maneig de l'osteoporosi

Tant la DMO com la microarquitectura i la qualitat òssies juguen un paper important en la resistència òssia i la susceptibilitat de sofrir una fractura. Tot i així, des d'un punt de vista clínic, el diagnòstic d'osteoporosi es basa en la DMO, segons les categories diagnòstiques de l'OMS (WHO) (Table 1.6). És important, però, diferenciar la definició operativa d'osteoporosi establerta d'aquest manera, de l'avaluació del risc de fractura i del llindar de tractament.

Actualment, no existeix cap guia universalment acceptada pel cribratge poblacional dels individus amb alt risc de fractura, essent la majoria identificats oportunísticament en presència d'una fractura per fragilitat o altres factors de risc. Quan la probabilitat de fractura basada en els factors de risc clínic és elevada, es recomana tractament independentment del valor de la DMO, mentre que l'estudi de la mateixa esdevé més decisiu en aquells casos on la probabilitat de fractura és intermitja. Finalment, els individus categoritzats de baix risc, no requeririen avaluació amb DMO o intervenció farmacològica (Figure 1.4). Algoritmes de predicció de fractura com el FRAX® poden facilitar aquesta presa de decisions. En darrer terme, caldrà tenir en compte factors geogràfics (com l'accés a aparells de DXA i el cost-benefici de les intervencions) i individuals (comorbiditats, adherència al tractament, etc).

Un cop identificats aquells subjectes candidats a intervenció farmacològica, caldrà també fer un cribratge inicial de causes secundàries d'osteoporosi i una anàlisi de l'estat de salut general prèviament a l'inici del tractament (Table 1.7).

La immobilització prolongada (com les esdevenides en llargues hospitalitzacions) constitueix una causa important de deteriorament de l'òs i cal que s'eviti en la mesura del possible, així com el risc de caigudes, que cal evaluar sistemàticament en cada subjecte (Table 1.8).

Un bon nivell d'activitat física, a més d'una ingesta adequada de calci, vitamina D (un mínim de 800 UI diàries en dones postmenopàusiques) i proteïnes, es

necessària per evitar la sarcopènia i l'osteoporosi relacionades amb l'edat (Rizzoli, Stevenson et al. 2014) .

Diversos agents farmacològics han estat aprovats pel tractament de l'osteoporosi. Tots ells han demostrat el seu efecte positiu sobre la DMO i la reducció en el risc de fractura (Table 1.9). Reduccions en el risc de fractura s'han demostrat entre un 30% i un 70 % per fractures vertebrals, al voltant d'un 15-20 % per fractures no vertebrals i fins a un 40% en fractures de maluc (Kanis, McCloskey et al. 2013). La reducció en la mortalitat s'ha estimat en un 11% a nivell mundial en una metanàlisi recent (Bolland, Grey et al. 2010). El cost-efectivitat ha estat ben establert de forma individual per tots aquests tractaments, així com també per estratègies de cribratge d'osteoporosi seguides d' intervenció farmacològica (Schousboe, Ensrud et al. 2005; Mobley, Hoerger et al. 2006; Hiligsmann, Gathon et al. 2010; Nayak, Roberts et al. 2011).

L'objectiu del tractament farmacològic és millorar la resistència òssia i conseqüentment reduir el risc de fractura. És possible que l'eficàcia anti-fracturària a llarg termini sigui només parcialment depenent de l'extensió en què augmenten o mantenen la DMO (Rabenda, Bruyere et al. 2011). De tota manera, com ja s'ha esmentat prèviament, la DMO és un dels majors predictors de resistència òssia, i constitueix una mesura objectiva, no invasiva i fàcilment reproduïble per monitoritzar els canvis amb el tractament. A més a més, existeix evidència científica de la correlació entre canvis en la DMO i reducció en el risc de fractura (Hochberg, Greenspan et al. 2002; Delmas, Li et al. 2004).

1.7 Osteoporosi en el món real: infradiagnosticada i infratractada

Els costos econòmics derivats de les fractures per fragilitat, tal com s'ha explicat prèviament, són enormes, i les projeccions basades en l'envelliment global de la població preveuen grans increments en la factura que les societats hauran d'afrontar en les properes dècades.

El cribratge i tractament dels pacients amb alt risc de fractura ha demostrat ésser cost-efectiu per diverses intervencions relativament senzilles (Strom, Borgstrom et al. 2007; Zethraeus, Borgstrom et al. 2007; Nayak, Roberts et al. 2012; Strom, Borgstrom et al. 2013). Com a factor de risc, la baixa DMO té un valor predictiu comparable al de la hipertensió arterial pels accidents cerebrovasculars o la hipercolesterolèmia per l'infart agut de miocardi (Marshall, Johnell et al. 1996). La intervenció terapèutica de tots tres factors de risc ha demostrat ser cost-efectiva a nivell poblacional, però el que és més important, el cost-efectivitat del tractament de l'osteoporosi millora clarament amb l'edat, la qual cosa no esdevé tan constant en el cas de la hipertensió o la hipercolesterolèmia (Zethraeus, Strom et al. 2008).

Aquestes observacions contrasten significativament amb la manca de cribratge de l' osteoporosi en la població general i la gran insuficiència de tractament després de la fase aguda d'una fractura per fragilitat (Strom, Borgstrom et al. 2013), amb menys d'un 20% de pacients rebent cap tipus d'intervenció farmacològica per prevenció secundària d'osteoporosi en el moment de l'alta hospitalària (Elliot-Gibson, Bogoch et al. 2004; Giangregorio, Papaioannou et al. 2006). Molt diferent és el cas, per exemple, de la gent gran amb infart agut de miocardi, 75% dels quals reben

betablocadors a l'alta com part de la prevenció secundària de cardiopatia isquèmica (Austin, Tu et al. 2008), i que il·lustra el gran recorregut en estratègies de prevenció i salut pública que l'osteoporosi ha de realitzar en comparació, per exemple, amb els factors de risc cardiovascular. Un paradigma d'aquest fet és la no menció de l'osteoporosi o les fractures per fragilitat entre les prioritats recentment establertes per l'OMS en malalties no comunicables (www.who.int).

1.8 Context d'aquesta tesi doctoral: "The Global Burden of Diseases 2010 Study"

El treball d'aquesta tesi constitueix part de les tasques realitzades pel grup expert en malalties musculoequelètiques (*Musculoskeletal Expert Group*, MSK EG) (Figure 1.9) (Cross M, Smith E et al. 2014; Driscoll, Jacklyn et al. 2014; Hoy D, March L et al. 2014; Hoy D, March L et al. 2014; Hoy D, Smith E et al. 2014; Hoy D, Smith E et al. 2014; Sanchez-Riera L, Carnahan E et al. 2014; Smith E, Hoy D et al. 2014; Smith, Hoy et al. 2014) dins la gran iniciativa en epidemiologia mundial coneguda com el *Global Burden of Disease (GBD) 2010 Study* (Vos, Flaxman et al. 2012; Lim, Vos et al. 2012; Murray, Vos et al. 2012; Salomon, Vos et al. 2012). Aquesta iniciativa es va iniciar el 1990 com un projecte de l'OMS per calcular la càrrega en salut mundial (*global*) de les principals malalties i condicions patològiques. El projecte GBD utilitza una eina d' estadística bayesiana (DisMod-MR, de l'anglès *Disease Modelling Meta-Regression tool*) especialment dissenyada pels propòsits del projecte i que permet comparar els paràmetres de mesura d'impacte (càrrega en salut) entre diferents malalties, regions del món, edats, i gèneres, així com analitzar tendències temporals. Les dues mesures principals de la càrrega en salut són les

morts i els anys de vida ajustats per discapacitat (*Disability-Adjusted Life Years*, DALYs), que combinen en una mateixa mesura els anys viscuts amb discapacitat (*Years Lived with Disability*, YLDs) i els anys de vida perduts degut a una mort prematura (*Years of Life Lost due to premature mortality*, YLLs) (Figure 1.8) (Murray, Vos et al. 2012). En l'edició 2010, múltiples millores en la metodologia de l'estudi GBD es van optimitzar respecte edicions prèvies, i el ventall de condicions es va ampliar significativament, abastant 291 malalties i lesions i 67 factors de risc (Murray, Vos et al. 2012).

L'osteoporosi, per si mateixa, no es trobà inclosa com a malaltia en l'estudi GBD 2010, i per primer cop, la baixa DMO (*low bone mineral density*, *low* BMD) s'inclogué en l'anàlisi de la càrrega en salut mundial com a factor de risc de fractures, que al seu torn, formaren part de la càrrega degut a les caigudes com a una de les 291 condicions estudiades en l'estudi GBD (Figure 1.11). Aquest treball descriu els mètodes utilitzats per calcular la contribució de la baixa DMO en la càrrega en salut mundial degut a les caigudes i presenta els resultat obtinguts per grups d'edat, gènere, i regió mundial, amb les estimacions obtingudes pel 1990 i pel 2010. La metodologia es basa en l'anàlisi de risc comparatiu (*Comparative risk assessment*, CRA), seguint la metodologia general per l'anàlisi de factors de risc dins l'estudi GBD 2010 (Lim, Vos et al. 2012).

2 Hipòtesis i Objectius

2.1 Hipòtesis:

1) Un percentatge important de la càrrega en salut mundial degut a les caigudes és potencialment evitable en un escenari hipotètic on la població d'edat avançada presenta un nivell de DMO ideal.
2) La càrrega en salut mundial degut a la baixa DMO ha augmentat probablement en els darrers 20 anys, degut particularment a l'envelliment de la població. La càrrega en salut de la baixa DMO pot variar en funció de la regió del món, el grup d'edat i el gènere.

2.2 Objectius:

1) Calcular els valors de DMO mesurats per DXA a coll femoral en la població mundial a partir dels 50 anys com la variable de risc d'exposició pel 1990 i pel 2010.
2) Calcular la fracció de la càrrega en salut mundial degut a les caigudes atribuïble a la baixa DMO pel 1990 i pel 2010.

3) Calcular el percentatge de la càrrega mundial en salut atribuïble a la baixa DMO pel 1990 i pel 2010.
4) Calcular el nombre total de morts arreu del món degudes a una baixa DMO pel 1990 i pel 2010.
5) Calcular el número de DALYs al món deguts a la baixa DMO pel 1990 i pel 2010.
6) Comparar la càrrega en salut mundial de la baixa DMO amb l'impacte derivat d'altres factors de risc dins l'estudi GBD 2010.

3 Mètodes

3.1 Introducció a l'Anàlisi de Risc Comparatiu ("Comparative Risk Assessment methodology")

En l'anàlisi de risc comparatiu (*Comparative Risk Assessment,* CRA) (Ezzati, Hoorn et al. 2011; Lim, Vos et al. 2012), l'impacte en salut degut a un factor de risc es compara a l'impacte hipotètic que resultaria si la distribució en la població del factor de risc es trobés a un nivell òptim (exposició "contrafactual"). Aquesta distribució "ideal" és el que es coneix com la distribució de risc teorèticament mínim (*theoretical-minimum-risk exposure Distribution,* TMRED), la qual ha de ser hipotèticament possible segons l'evidència científica disponible (Figure 3.1):

$$PAF = \frac{\int_{x=0}^{m} RR\,(x)P(x)dx \; - \; \int_{x=0}^{m} RR\,(x)P'(x)dx}{\int_{x=0}^{m} RR\,(x)p(x)dx}$$

Seguint la fòrmula anterior, es calcula la fracció poblacional atribuïble (*Population Attributable Fraction*, PAF), on *RR(x)* és el risc relatiu segons l'exposició al factor de risc *x*, *P(x)* és la distribució poblacional de l'exposició al factor de risc, *P'(x)* és la distribució contrafactual de l'exposició al factor de risc, i *m* es el nivell d'exposició màxima al factor de risc. Utilitzant aquesta metodologia, s'ha estimat quina proporció de la càrrega en salut mundial degut a les caigudes en la població mundial es

atribuïble a la baixa DMO, seguint els passos metodològics que es detallen a continuació.

3.2 Constitució del grup de treball per Osteoporosi en l' estudi GBD 2010

Aquest treball s'ha dut a terme amb la contribució d'una xarxa de professionals internacionals que han treballat en equip amb diversos graus d'involucrament. El projecte es nodreix d'aquesta xarxa de col·laboració per tal de produir una metodologia i analitzar els resultats de la manera més adequada possible, amb la guia d'experts en epidemiologia de l'osteoporosi i en salut pública mundial. Així, es va crear el grup de treball en osteoporosis (*Osteoporosis Working Group*, OWG), el qual es trobava dividit en l'equip revisor (*Review Team*, RT) i el grup de líders experts (*Expert Leaders Group*, ELG). Aquest darrer es trobava format tant per experts en salut publica implicats directament en l'estudi GBD 2010 com per líders d'opinió mundial en epidemiologia de l'osteoporosi. Tots els passos en la metodologia així com els resultats provisionals foren supervisats per coordinadors generals en el grup d'experts de malalties musculoesquelètiques (*MSK EG group*) i membres de l'equip central (*core team*, CT) de l'estudi GBD 2010 a la Universitat de Washington, per tal de proporcionar resposta a les dificultats i assegurar l'homogeneïtat dins l'estudi (Table 3.1).

La líder del OWG, (*main project officer*, MPO) realitzà el cribratge dels resultats obtinguts de la SR per obtenir el número final d'estudis seleccionats per ser inclosos, liderà el procés d'extracció de dades, proporcionà evidencia científica a

l'ELG per facilitar les discussions de grup quan fou necessari, coordinà reunions i comunicacions dins de cada grup i entre grups, liderà l'escriptura de manuscrits científics, i presentà comunicacions en congressos internacionals (Figure 3.2).

3.3 Definició de la variable d'exposició al factor de risc. Extracció i gestió de dades

Es va realitzar una revisió sistemàtica (*systematic review*, SR) a través de les bases de dades Medline, Embase, CAB Abstracts, CINHAL, WHOLIS, i SIGLE, cercant estudis poblacionals publicats entre el 1980 i el 2010 amb valors de DMO en g/cm^2 mesurats amb DXA a coll femoral (*femoral neck bone mineral density*, FNBMD). En regions amb molta escassetat de dades també es van incloure altre tipus d'estudis (no poblacionals) sempre i que la mostra es considerés mínimament representativa de la població nacional. La DXA central es la tècnica mes validada per mesurar la DMO. La localització concreta a coll femoral (FNBMD) es va justificar per l'evidència existent de que la predicció de la morbiditat i mortalitat relacionades amb la fractura de maluc (la fractura osteoporòtica amb les conseqüències més nocives per la salut) és òptima quan la DMO és mesurada a coll femoral enlloc de columna o radi distal (Johnell, Kanis et al. 2005). El que és més, les mesures de FNBMD es troben molt ben correlacionades amb el risc de fractura vertebral, amb altres fractures osteoporòtiques i amb qualsevol fractura en general (Johnell, Kanis et al. 2005).

La MPO va dissenyar una base de dades en MS Excel que, després de la seva revisió dins el OWG, va ser implementada per extraure les dades dels estudis seleccionats a la SR, i que incloïa els següents paràmetres: regió mundial, país, any

de publicació, tipus d'estudi, tamany de la mostra, descripció de la població d'estudi, cobertura (rural, urbana o ambdues), any d'inici i final de col·lecció de dades, edat dels participants, raça, marca del fabricant de la DXA, coeficient de variació (CV) de la mesura de la DMO a coll femoral (FNBMD), mitja dels valors de FNBMD en g/cm^2 i DE (SD). Tots els estudis inclosos es van sotmetre a una avaluació de qualitat amb una eina per mesurar el risc de biaix (*risk of bias tool*, RoB tool) validada anteriorment per estudis de prevalença (Hoy, Brooks et al. 2012) i modificada a traves d'exercicis Delphi pels propòsits de la revisió en baixa DMO (Sanchez Riera, Wilson et al. 2010). Tots els valors de les mitges i SD de FNBMD provinents de diferents fabricants de DXA (Hologic®, Norland® i Lunar®) foren estandarditzats a través d' equacions de conversió internacionalment reconegudes (Table 3.2) (Lu, Fuerst et al. 2001) a sFNBMD i sSD, respectivament. Finalment, es va realitzar un cribatge sistemàtic de les dades per identificar duplicats i inconsistències en els valors.

Les mitges de sFNBMD i sSD per cada regió, país i any es van calcular fent servir DisMod-MR, una eina d'estadística bayesiana dissenyada específicament pels propòsits de l'estudi GBD 2010 (Vos, Flaxman et al.). El model incloïa efectes fixos per co-variables dependents de l'estudi, i efectes aleatoris segons la regió mundial i el país.

Amb l'ús de DisMod-MR, covariables a nivell nacional de les quals es disposés àmplia informació a la major part de països del món, es podien utilitzar per predir valors aproximats de DMO en aquelles regions amb una manca important de dades. Així, es van utilitzar els ingressos lag-distribuït per habitant, l'índex de massa

corporal (*body mass index*, BMI), i la disponibilitat de llet basada en dades de la *Food and Agriculture Organization* de les Nacions Unides com les covariables nacionals. Altres estratègies per obtenir dades en regions amb manca d'informació sobre nivells poblacionals de DMO va incloure el contacte directe amb alguns dels autors dels estudis inclosos i professionals relacionats amb el món de l'osteoporosi per tal d'obtenir informació no publicada.

3.4 Avaluació de la relació de risc entre baixa DMO i fractura

Les nostres estimacions del risc relatiu (RR) entre DMO i fractures es basen en una metanàlisi publicada el 2005 de 12 estudis poblacionals prospectius d'Europa occidental, Estats Units, Canadà, Japó i Austràlia (Johnell, Kanis et al. 2005). El nostre SR també incloïa una cerca dissenyada per identificar estudis d'alta qualitat en risc relatiu entre DMO i fractura. (Figure 4.1). Es van identificar molts pocs estudis poblacionals prospectius publicats després de la metanàlisi del 2005 (Table 4.2), els quals presentaven valors de RR comparables als obtinguts prèviament, amb una mostra total poc significativa comparat amb la metanàlisi anterior, i per tant, es va considerar com no necessària l'actualització de la metanàlisi del 2005.

Pels objectius del nostre treball, els valors originals de RR expressats en RR/SD del Z score, es van transformar a valors absoluts de RR/0,1g/cm^2 de FNBMD (Table 3.3), amb la col·laboració d'un dels autors de la metanàlisi, que era un dels membres components de l'ELG, i de l'ús de DisMod-MR, que en va derivar estimacions de risc per homes i dones per cada grup d'edat, tant per fractures de maluc, com per la resta de fractures en el seu conjunt.

Per establir el TMRED (el nivell òptim de DMO), es va escollir una referència internacional que permetés realitzar comparacions, provinent de la mostra poblacional del *National Health and Nutritional Examination Survey* (NHANES) III (Looker, Wahner et al. 1998). Després d'analitzar el resultat provisional de diversos escenaris de TMRED (Figure 3.3 i Figure 3.4), es va decidir finalment per l'ús del percentil 90 específic per edat i gènere de caucàsics d'aquest estudi (Table 3.4).

3.5 Càrrega en salut mundial degut a les caigudes atribuïbles a la baixa densitat mineral òssia

La mortalitat i la morbiditat associades a la baixa DMO es van calcular, només, per poblacions a partir dels 50 anys. Els principals motius foren la relativa baixa prevalença de la condició en poblacions més joves, i sobretot, la manca d'una evidència epidemiològica sòlida de la relació DMO-fractura en poblacions més joves.

La informació en mortalitat en l'estudi GBD 2010 es va obtenir de diverses fonts, de les quals les més importants foren els registres vitals nacionals i les morts intra-hospitalàries (Lozano, Naghavi et al. 2012). Per atribuir les morts degudes a baixa DMO, la dificultat estrebava en que les morts es trobaven categoritzades segons la causa de la lesió (caigudes), enlloc de la naturalesa de la lesió (fractura). Al seu torn, les fractures es poden trobar com a conseqüència de moltes lesions segons el sistema internacional de classificació de malalties (*International Diseases Classification System and other health problems*, ICD), com ara accidents de trànsit, assalts, o desastres naturals. Degut als objectius de la nostra anàlisi, les estimacions de les PAFs es van restringir a aquelles fractures degudes a caigudes

“casuals” o accidentals”, on s’esperava trobar-hi la major part de les fractures degudes a osteoporosi o baixa DMO. Amb aquest propòsit, es van utilitzar registres nacionals de dades hospitalàries de Brazil (Ministry of Health (Brazil). 2006-2009), Canadà (Canadian Institute for Health Information. 1994-2009), Mèxic (Ministry of Health (Mexico). 2000-2009), i els Estats Units (National Center for Health Statistics, Centers for Disease Control and Prevention, US Census Bureau. 1979-2009) amb doble codificació (causa i naturalesa de la lesió) per calcular la proporció de morts intra-hospitalàries degudes a caigudes que involucressin fractures de maluc o fractures vertebrals. Aquelles caigudes amb menció concomitant de dany cerebral o lesió interna (sagnat abdominal, hemotòrax, etc) es van excloure de l’anàlisi. Altres tipus de fractura (no-maluc-no-vertebral) es van excloure dels càlculs, ja que es van considerar com menys probables de causar mortalitat, decisió recolzada per una anàlisi de la base nacional de dades australiana (http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3303.0Main+Features12003?OpenDocument). Atès que aquesta era l’única font per determinar la fracció de les morts secundàries a caigudes degudes a fractures de maluc o vèrtebra, fou necessari aplicar les proporcions obtingudes a tots els països.

Pel que fa al càlcul de la discapacitat, els YLDs es van calcular segons la localització de la fractura en totes aquelles fractures resultants de caigudes accidentals, amb dades d’incidència provinent fonamentalment d’altes hospitalàries de planta i urgències. D’aquesta manera, els RRs per unitat de FNBMD relacionats amb fractura de maluc (Table 3.3) es van aplicar a totes les fractures de maluc, mentre que el RRs de fractures diferents del maluc es van aplicar a la resta de fractures (Table 3.3). Pel càlcul dels YLDs es van utilitzar els pesos relatius de

discapacitat (*Disability Weights*, DW) originats en l'estudi GBD 2010 per cada localització de fractura(Table 3.6) (Salomon, Vos et al. 2012).

El resultat de les PAFs de baixa DMO per fractures foren aplicats als càlculs de YLDs de les fractures dins la càrrega global degut a les caigudes. Pels càlculs de mortalitat, les PAFs per fractures foren aplicades a les proporcions de morts relacionades amb caigudes per fractures de maluc i fractures vertebrals sense fractura de maluc (Table 3.5).

Finalment, per obtenir el número de DALYs finals deguts a baixa DMO es van aplicar les fòrmules generals relacionades amb el GBD:

DALY= YLL + YLD

on:

YLL=*years of life lost to premature mortality* ; **YLD**=*years lived with disability*

i:

YLL = N x L

on N = *number of deaths*; **L** = *standard life expectancy at age of death in years*

4 Resultats

4.1 Resultats de la revisió sistemàtica

El procés de revisió sistemàtica (SR) es mostra a la Figure 4.1. Es van seleccionar 130 estudis (Appendix 5) per la variable d'exposició de risc (FNBMD), amb un total de 860 punts d'informació provinent de 49 països de 17 de les 21 regions en què es va dividir el món en l'estudi GBD 2010 (Figure 4.2), amb una heterogeneïtat important en quant a la quantitat d'informació segons la regió. La dades sobre els nivells poblacionals de DMO foren més robustes pel 2010, ja que el nombre de publicacions va augmentar progressivament des del 1980 fins el 2010 (Figure 4.3).

Cap de les variables nacionals utilitzades (ingressos per habitant, índex de massa corporal, i disponibilitat de llet) va demostrar cap millora significativa en l'habilitat predictiva de DisMod-MR, i per tant, no foren incloses en el model de predicció.

L'eina per valorar la qualitat dels estudis inclosos (RoB tool) tampoc no va provar ser predictiva del valor de DMO (Table 4.1), i per tant, no es va introduir cap co-variant en l'anàlisi depenent del risc de biaix basat en els resultats del RoB tool.

Pel que fa a la segona estratègia de cerca (*risk factor-disease relationship*) (Figure 4.1), com s'ha esmentat anteriorment, es van identificar molts pocs estudis poblacionals prospectius publicats després de la metanàlisi del 2005 (Table 4.2).

Aquests estudis presentaven valors de RR comparables als obtinguts prèviament, amb una mostra total poc significativa comparat amb la metanàlisi anterior, i per tant, es va considerar com no necessària l'actualització del metanàlisi del 2005.

4.2 Resultats de la variable d'exposició al factor de risc: Distribució de la densitat mineral òssia

La distribució mundial dels valors poblacionals de la DMO (expressat en sFNBMD) a partir dels 50 anys d'edat pel 1990 i pel 2010 es mostra en la Figure 4.6. Àsia i Àfrica foren les regions amb nivells més baixos de DMO, mentre que Nord-Amèrica, la regió del Carib i Europa de l'est mostraren els valors més elevats de DMO tant per homes com per dones. Malgrat que els valors de DMO ajustats per edat havien mostrat una tendència a la millora entre 1990 i 2010 en anàlisis descriptives preliminars (Sanchez-Riera, Wilson et al. 2010), particularment a Àsia i Europa occidental, la DMO a nivell poblacional disminuí en algunes regions degut a l'envelliment de la població.

4.3 Fracció de la càrrega en salut mundial degut a caigudes atribuïble a la baixa densitat mineral òssia

La fracció de l'impacte degut a caigudes atribuïble a la baixa DMO (PAFs) resultà en general més elevada en dones que en homes, tant per les estimacions del 1990 com per les del 2010. En general, les PAFs més altes s'observaren en regions pobres (Àsia est, Àsia sud-est, Àfrica sub-sahariana est i oest), amb l'excepció de l'Europa de l'est. No obstant, gran diversitat de PAFs s'observà entre els països rics,

fins i tot dins la mateixa regió geogràfica (els països escandinaus, per exemple, comparats amb el Regne Unit) (Figure 4.7).

Pels càlculs de 1990, un 12,1% de tots els DALYs deguts a caigudes i un 29,6% de totes les morts degudes a les caigudes foren atribuïbles a la baixa DMO. Aquests percentatges augmentaren al 14,8% i al 34,7%, respectivament, per les estimacions del 2010. La contribució en la càrrega mundial entre totes les causes de salut s'incrementà en totes les regions mundials excepte el Carib i Oceania (Table 4.3).

4.4 Càrrega en salut mundial degut a la baixa densitat mineral òssia: DALYs, YLDs, YLLs i morts

A nivell mundial, el número de morts i de DALYs atribuïbles a la baixa DMO pel 1990 augmentà des de 103.000 i 3.125.000, respectivament, a 188.000 i 5.216.000, respectivament, pel 2010. La contribució de la baixa DMO en la càrrega en salut mundial resultant de totes les causes analitzades gairebé es duplicà des del 1990 (0,12%) fins al 2010 (0,21%), amb augments significatius tant dels YLLs com dels YLDs en ambdós sexes (Table 4.4). En el grup d'edat de 50-69 anys, aquests percentatges incrementaren al 0,41% pel 1990 i al 0,5% pel 2010, i esdevingueren encara més elevats en la població a partir dels 70 anys d'edat (0,64% i 0,79%, respectivament) (http://www.healthdata.org/gbd). Àsia est i Àsia sud foren les regions que més van contribuir a l'increment mundial de l'impacte en salut de la baixa DMO. Les tasses de DALYs mundials per 100.000 habitants augmentaren significativament des 1990 al 2010, però l'augment fou més discret amb l'estandardització per edat (Table 4.3), la qual cosa reflecteix el creixement i

envelliment de la població. Les tasses foren més altes a Europa occidental, Europa central, i la regió Àsia-Pacífic, mentre que les tasses estandarditzades per edat foren més altes, en general, en regions en vies de desenvolupament o subdesenvolupades, tals com Àfrica subsahariana est i oest, Oceania, Àsia est, i Àsia sud (Table 4.4 i Figure 4.8). La mortalitat prematura (YLLs) contribuí a la càrrega mundial en salut lleugerament més que la discapacitat (YLDs). Així, els YLLs representaren el 51% i el 53% de tots els DALYs atribuïbles a la baixa DMO pel 1990 i pel 2010, respectivament (Table 4.4).

L'anàlisi per gèneres rebel·là que els homes obtingueren més DALYs que les dones tant pel 1990 com pel 2010, amb una bretxa entre els dos gèneres que augmentà entre els dos períodes, corresponent un 56% i un 60% de tots els DALYs als homes pel 1990 i el 2010, respectivament (Table 4.4). La bretxa entre gèneres augmentà amb el càlcul de la tassa de DALYs per 100.000 habitants tant pel 1990 com pel 2010, i en el subgrups de 50-69 anys i ≥ 70 anys. Les diferències entre sexes foren més destacables en els YLLs que en els YLDs. Les morts atribuïbles a la baixa DMO gairebé es doblaren en homes des del 1990 (52.816) al 2010 (103.440), mentre que en dones l'increment fou d'aproximadament un 60% entre el 1990 (50.455) i el 2010 (84.146) (http://www.healthdata.org/gbd).

Per totes les malalties, lesions i factors de risc analitzats en l'estudi GBD 2010, els detalls sobre els resultats dels DALYs, YLDs, YLLs i morts es poden visualitzar a la web de *l'Institute for Health Metrics and Evaluation* (IHME) de forma gratuïta per regió, país, gènere, grup d'edat i any (http://www.healthdata.org/gbd).

4.5 Comparació de la càrrega en salut de la baixa densitat mineral òssia comparat amb altres factors de risc en l'estudi GBD 2010.

La baixa DMO obtingué un rang més aviat baix en termes del total de DALYs que en foren atribuïbles en comparació amb altres factors de risc analitzats en l'estudi GBD 2010, com els factors dietètics, la pressió arterial elevada, el tabaquisme, l'ús de l'alcohol, la glucosa sèrica en dejú, l'alt IMC, l'alt colesterol i la baixa activitat física (Figure 4.9) (Lim, Vos et al. 2012).

En agrupar tots els factors dietètics i tots els factors ocupacionals en una categoria conjunta per cadascun, la classificació de la baixa DMO es trobà en la posició 20 entre 21 categories de factors de risc analitzats en les estimacions mundials pel 1990, i en la posició 23 entre 25 categories pel 2010. Per algunes regions del món, la baixa DMO ocupà posicions més elevades: la posició 12 a Europa Occidental, la 13 a Àsia-Pacífic, la 15 a Europa central, Australàsia i Nord-Amèrica, i la 16 a Àsia est. Una millora en la classificació mundial dels factors de risc s'observà en seleccionar els subgrups d'edat avançada (Figures 4.10-4.17). Així, per exemple, la baixa DMO fou l'11è factor de risc (d'entre 17 categories) amb el màxim nombre de DALYs al món pel 1990, i el 13è (entre 21 categories) pel 2010 (Figure 4.11) en població ≥ 70 anys. Els resultats foren similar per homes i dones, amb canvis màxims d'una posició en les classificacions per grups de gènere (http://www.healthdata.org/gbd).

5 Discussió

Les conseqüències en salut de les fractures osteoporòtiques van des del dolor crònic fins a la institucionalització i la mort, ocasionant una factura social i econòmica enormes, amb projeccions d'augmentar ràpidament en les properes dècades arreu del món. Atesa l'evidència de que el cribratge i tractament de l'osteoporosi és cost-efectiu, i la manca actual de reconeixement de la seva importància, iniciatives en salut pública són requerides urgentment per tal de promoure'n el diagnòstic precoç i el tractament.

Per primer cop, la baixa DMO, un bon predictor d'osteoporosi i risc de fractura, ha estat analitzada com a factor de risc dins l'estudi d'epidemiologia d'abast mundial GBD 2010. La càrrega en salut atribuïble a la DMO s'ha realitzat analitzant el seu impacte en les fractures, que al seu torn, han format part de la càrrega en salut deguda a les caigudes.

Els resultats han mostrat que, tot i que els valors de la DMO ajustats per edat mostraren una tendència a la millora a nivell mundial a través del temps, l'impacte absolut en salut de la baixa DMO augmentà del 1990 al 2010, probablement relacionat al creixement global de la població d'edat avançada. Les tasses de DALYs estandarditzades per edat i les PAFs més elevades en regions mundials pobres probablement reflecteixen el paper important de determinants de la DMO potencialment modificables, com els factors nutricionals i l'accés a l'assistència sanitària. La mortalitat prematura (YLLs) contribuí lleugerament més que la

discapacitat (YLDs) en el conjunt global de DALYs atribuïbles a baixa DMO. Aquest fet s'explica, al menys parcialment, per l'alta mortalitat associada, ja que la baixa DMO podria ésser responsable de fins a un terç de totes les morts atribuïbles a les caigudes accidentals, les quals ocuparen la tercera posició entre les lesions amb més càrrega en salut mundial en el GBD 2010 (la segona posició en el grup de 50-69 anys i la primera posició en el grup a partir de 70 anys) (Murray, Vos et al. 2012).

Per tots els paràmetres de mesura de l'impacte en salut, els homes mostraren valors més elevats que les dones malgrat les PAFs foren superiors en les darreres. Raons que expliquen aquesta troballa són la incidència més alta de fractures en el conjunt d'homes, i la tassa de mortalitat més elevada en homes seguint la fractura, particularment en els grups d'edat més joves. Aquesta darrera observació és compatible amb estudis longitudinals (Center, Nguyen et al. 1999, Kannegaard, van der Mark et al. 2010, Melton, Achenbach et al. 2013). La inclusió de totes les localitzacions de fractures, incloent aquelles no clarament relacionades amb l'osteoporosi (cara, crani, mà) i el ventall ampli de codis de caigudes utilitzats (incloent lesions per traumatismes d'alta energia) es l'explicació més raonable darrera de la superioritat de la càrrega en salut atribuïble a la baixa DMO en homes comparat amb dones, conjuntament amb la utilització d'un TMRED per l'anàlisi de risc comparatiu que pretenia eliminar l'efecte de l'edat i el gènere en el risc de fractura.

Tot i que el pes relatiu de la baixa DMO comparat amb la resta de factors de risc augmentava en grups d'edat avançada i en regions desenvolupades, en global,

l'impacte de la baixa DMO en el total de la salut mundial esdevingué inferior a molts altres factors de risc, i és possible que el pes relatiu de la DMO en el panorama de la salut mundial hagi estat infravalorat per diverses raons.

Primer, l'elecció d'un nivell òptim de DMO (TMRED) per l'anàlisi de risc comparatiu (CRA) utilitzant una referència ajustada per edat i gènere, emmascarà l'important paper de l'edat i el gènere en el risc de fractura (Kanis, Johnell et al. 2001), i pot ser que expliqui una gran part del pes relativament baix que la baixa DMO obtingué en comparació a altres factors de risc dins l'impacte en salut mundial. Tanmateix, la iniciativa GBD té com a objectiu principal la de proporcionar una fotografia útil per tal d'ajudar a establir prioritats en estratègies de salut pública; es centra sobretot en condicions "modificables". En conseqüència, l'edat i el gènere havien de ser exclosos de l'anàlisi atès el seu paper clar com factors de risc independents de baixa DMO. D'altra banda, l'elecció d'una referència caucàsica americana (Looker, Wahner et al. 1998) per dibuixar l'escenari ideal de DMO pot haver conduït a una sobreestimació o una infraestimació, segons la regió, del paper de la baixa DMO en l'impacte en salut. En aquest sentit, l'ús de diversos TMREDs regionals foren considerats. No obstant, es va seleccionar una referència única, l'actualment recomanada pels organismes científics internacionals (Kanis 2008; Kanis, McCloskey et al. 2008; Internaional Society of Clinical Densitometry 2013) per tal de facilitar l'anàlisi comparatiu entre diferents regions del món. A més a més, no existia una referència poblacional d'alta qualitat per cada regió del món. A banda de totes aquestes consideracions en relació al TMRED per la nostra anàlisi de risc comparatiu, el que és important de remarcar és que la relació de risc entre DMO i

fractures sembla ser constant entre diverses ètnies (Leslie 2012; Shin, Zmuda et al. 2014).

Separar les morts degudes a fractures del global de morts relacionades amb les caigudes no fou una tasca fàcil. Va ser necessari recórrer a les poques fonts que informaven tant de la causa de la lesió com de la naturalesa de la lesió a través de dades hospitalàries que incloïen la doble codificació segons els sistemes ICD9 i ICD 10. Tampoc fou gens fàcil atribuir morts com a conseqüència de fractures a la baixa DMO, ja que rarament els diagnòstics d'osteoporosi, osteopènia o baixa massa òssia apareixien en els certificats de defunció. Per resoldre aquests conflictes, es van incloure totes aquells codis de caigudes potencialment relacionats amb "fractures per fragilitat", segons la definició de les quals, succeeixen de forma inintencionada com a conseqüència d'un succés intrínsec no major (Gibson M 1987). Tot i que alguns pocs codis podien incloure caigudes potencialment d'alt impacte, i per tant, no considerades clàssicament com caigudes relacionades amb "fractures per fragilitat", es considerà que també compartien en tot cas una relació amb la baixa DMO. Una altra estratègia rellevant per identificar aquelles morts potencialment relacionades amb la fractura i la baixa DMO fou excloure aquells traumatismes amb codis concomitants corresponents a lesió cerebral o interna, per facilitar l'anàlisi de mortalitat degut únicament al succés de la fractura.

Assumir que només les fractures associades a caigudes accidentals es trobaven relacionades amb la baixa DMO ben segur fou una causa de pèrdua de l'impacte estimat per la baixa DMO en la salut global, atesa l'evidència prèvia del paper rellevant de la DMO tant en traumatismes de baixa com d'alta energia (Karlsson,

Hasserius et al. 1993; Sanders, Pasco et al. 1998; Mackey, Lui et al. 2007), inclús en població jove. Si es consideren, per exemple, totes les fractures relacionades amb accidents de trànsit i les autolesions (primera i segona causes d'impacte en salut mundial pel que fa al grup de lesions en l'estudi GBD 2010), el percentatge potencial de l'impacte en salut degut a la baixa DMO que s'ometé és immens.

D'altra banda, només les fractures clíniques (aquelles que resulten de caigudes) es tingueren en compte en les estimacions de l'impacte de la baixa DMO, mentre que és ben reconegut que només al voltant d'un terç de les fractures vertebrals són clíniques (Ross 1997). Les fractures vertebrals prevalents, inclús si tenen lloc sense símptomes aguts, comporten freqüentment conseqüències a llarg termini, com dolor crònic, cifosis i patologia pulmonar restrictiva (Silverman 1992; Ross 1997). Per bé que és d'esperar que la càrrega en salut d'aquest tipus de fractura fou recollit en part dins el ventall de condicions subjacents a la lumbàlgia (*low back pain*, primera causa de discapacitat mundial en l'estudi GBD 2010), cal admetre la seva exclusió dins l'impacte en salut degut a les caigudes, i per tant, la reducció en el paper atribuïble de la DMO.

La troballa de més YLLs que YLDs en els resultats d'aquest treball és contrària a la noció que la major part de l'impacte en salut provinent de les fractures prové, precisament, de la discapacitat a llarg termini (ja que la major part d'inidividus no moren després de patir una fractura). Una explicació plausible darrera d'aquests resultats és el poc pes relatiu de la fractura de maluc en la seva descripció de seqüela a llarg termini (Table 3.6). És molt possible que el mot "*fixed*" ("arreglat") de la descripció utilitzada per generar-ne el DW corresponent indugués falsament a una

valoració excessivament optimista de la discapacitat a llarg termini de la fractura de maluc. Una altra possible font de pèrdua de YLDs és la utilització predominant de dades hospitalàries per detectar aquelles fractures relacionades amb caigudes, ja que és probable que algunes fractures menors en països no desenvolupats no acabin en consulta hospitalària.

L'exclusió de totes aquelles fractures diferents de la localització en maluc i vèrtebra de l'anàlisi de mortalitat relacionat a les fractures per caigudes fou probablement un altre factor contribuent a la infraestimació del paper de la baixa DMO en salut. Com s'explicà en la secció de mètodes, la inclusió exclusiva de les fractures de maluc i les fractures vertebrals es recolzà en un anàlisi prèvia de la base de dades nacionals de mortalitat australiana (http://www.abs.gov.au/ AUSSTATS/abs@.nsf/ Lookup/3303.0Main+Features12003?OpenDocument). Importants estudis epidemiològics longitudinals han trobat resultats similars (Cauley, Thompson et al. 2000; Ioannidis, Papaioannou et al. 2009). Per bé que les fractures de maluc i de vèrtebra han demostrat ser la primera i la segona causa de mortalitat, respectivament, degut a fractures osteoporòtiques (Browner, Pressman et al. 1996; Bliuc, Nguyen et al. 2009; Ioannidis, Papaioannou et al. 2009), alguns autors han demostrat la participació d'altres localitzacions de fractura en el risc de mortalitat a llarg termini en estudis prospectius (Bliuc, Nguyen et al. 2009; Morin, Lix et al. 2011; Melton, Achenbach et al. 2013; Bliuc, Nguyen et al. 2014). Malgrat això, bona part d'aquest excés de mortalitat es atribuïble al risc de subseqüents fractures amb alt impacte en salut, com la fractura de maluc. De fet, la mortalitat a llarg termini relacionada amb les fractures es un fenomen tediós d'interpretar en el marc de l'estudi GBD, ja que la mortalitat ha de trobar-se intrínsecament associada a la

fractura. Això pot resultar difícil d'interpretar, sobretot tenint en compte que la mortalitat relacionada a les fractures osteoporòtiques es troba molt íntimament relacionada als nivell basals de fragilitat (Cawthon, Marshall et al. 2007; Ensrud, Ewing et al. 2007; Tosteson, Gottlieb et al. 2007; Patel, Brennan et al. 2014), i per tant, esdevé complicat establir quina fracció d'aquesta mortalitat a llarg termini és realment atribuïble al succés de la fractura.

Pel que fa al mètode de mesura de la variable d'exposició al factor de risc, la DXA, cal acceptar un possible biaix de selecció envers a països amb més àmplia disponibilitat d'aquesta tècnica (International Osteoporosis Foundation 2008). A més, l'aplicació d'equacions d'estandardització entre diferents fabricants de DXA resulta probablement incompleta per eliminar totes la diferències de mesura entre aparells, especialment entre diferents models del mateix fabricant (Barthe, Braillon et al. 1997; Henzell, Dhaliwal et al. 2003). D'altra banda, la selecció del coll femoral com a única localització de la mesura de la DMO també pot haver infraestimat la prevalença de la baixa DMO, davant l'observació que els nivells de DMO a columna lumbar solen ser en general més baixos que a maluc, sovint presentant discordança diagnòstica (Woodson 2000; O'Gradaigh, Debiram et al. 2003; Looker, Melton et al. 2012). Ara bé, les mesures de la DMO a columna lumbar tenen més risc d'ésser artefactades (sobretot per canvis artròsics o calcificacions vasculars) que no pas a coll femoral (Paggiosi, Glueer et al. 2011). El que és més, fins al moment, l'evidència epidemiològica més robusta en relació al risc relatiu DMO-fractures utilitza la DMO a coll femoral (FNBMD) com a variable d'exposició al risc (Johnell, Kanis et al. 2005).

En tant a la qualitat dels estudis que finalment es van incloure de la revisió sistemàtica, no es trobà cap diferència en els valors de DMO entre diferents grups de risc de biaix. Eren esperables, per exemple, les divergències entre diferents grups de risc de biaix de selecció, ja que gran part dels estudis excloïen individus amb història de fractura prèvia, però els models de regressió lineal no van aconseguir de demostrar aquesta hipòtesi. Les raons darrera d'aquest resultats són desconegudes, però és possible que tingui relació amb la disparitat en número d'estudis en cada grup de biaix, i l'heterogeneïtat entre els estudis en general.

Finalment, cal tenir en compte les limitacions intrínseques d'aquest treball. D'una banda, cal recordar que, malgrat la baixa DMO és un bon predictor del risc de fractura, té una baixa sensibilitat com a factor de risc aïllat (Siris, Chen et al. 2004). És possible que estudis futurs puguin utilitzar mesures compostes de la resistència òssia, incloent paràmetres de geometria de maluc, grossor cortical i trabecular, etc, a més a més de la DMO. Per ara, això no és possible d'aplicar a un nivell poblacional, i menys encara, en un estudi d'àmbit mundial, degut a una manca clara de la disponibilitat àmplia de la tecnologia necessària i de l'excés de radiació que aquestes tecnologies impliquen. Tot i així, la DMO constitueix encara una mesura fàcil i objectiva de mesurar la resistència òssia i que permet realitzar comparacions a molts nivells (entre edats, regions, etc). Ara bé, aquest treball boga per una anàlisi del risc de fractura basada en la DMO com una variable contínua, i no basada en les categories diagnòstiques establertes per l'OMS.

Per acabar, cal recordar les limitacions intrínseques relacionades amb l'abast de la l'estudi GBD. Aquesta iniciativa no té en consideració els costos socials i econòmics derivats de cada condició estudiada. Tal com s'ha explicat prèviament, les millores en l'expectativa de vida i l'envelliment mundial de la població estant conduint les fractures osteoporòtiques a provocar una factura enorme per gairebé totes les societats del món, amb projeccions de créixer ràpidament en les següents dècades i convertir-se en una de les verdaderes epidèmies de les societats futures. El cribratge i el tractament farmacològic de l'osteoporosi ha demostrat ser cost-efectiu per reduir-ne les fractures i la mortalitat derivades. Tot i així, la manca de reconeixement de la magnitud del problema és encara molt insuficient per part de la població general, els professionals en salut i les institucions científiques. Per tant, les autoritats en salut pública han de considerar tots aquests factors de gran rellevància en establir prioritats en prevenció de malalties i decidir on destinar els recursos.

6 Conclusions

Aquest treball constitueix el primer estudi mai realitzat en mesurar la càrrega en salut mundial que seria teòricament evitable en l'absència de baixa DMO a la població mundial, considerant la DMO com una variable contínua i utilitzant una metodologia única que permet comparar estimacions entre gèneres, grups d'edat i regions del món, i analitzar tendències amb el temps. El resultats obtinguts ens permeten arribar a les següents conclusions:

1. En la població a partir dels 50 anys d'edat, Àsia i Àfrica foren les regions del món amb valors més baixos de DMO a coll femoral (FNBMD), mentre que Nord-Amèrica, el Carib i Europa de l'est mostraren els valors de FNBMD més elevats, tant per homes com per dones. Tot i que els valors de FNBMD ajustats per edat mostraren una millora entre el 1990 i el 2010, sobretot a Àsia i Europa occidental, la distribució dels nivells poblacionals de FNBMD varen disminuir entre els dos períodes degut a un envelliment global de la població. Els nivells poblacionals de FNBMD foren superiors en homes que en dones per totes les regions mundials i per tots els períodes de temps.

2. La fracció poblacional atribuïble (PAFs) de la baixa DMO per les caigudes fou generalment més elevada per dones que per homes tant el 1990 com el 2010. En general, les PAFs més altes s'observaren en regions pobres (Àsia est i Àsia sud-est, Àfrica subsahariana sud-est, Àfrica subsahariana est i Àfrica subsahariana oest). Les PAFs mundials degudes a la baixa DMO van

augmentar des de 1990 al 2010 tant per homes com per dones. El nombre total de DALYs atribuïbles a la baixa DMO pel 1990 representaren un 12,1% i un 29,6%, respectivament, de tots els DALYs deguts a caigudes. Aquests percentatges augmentaren al 14,8% i al 34,7%, respectivament, per les estimacions del 2010.

3. El percentatge de la baixa DMO en la càrrega en salut mundial gairebé es doblà des del 1990 (0,12%) al 2010 (0,21%). En la població de 50-69 anys, aquests percentatges augmentaren al 0,41% pel 1990 i al 0,5% pel 2010, i foren encara més elevats en la població a partir dels 70 anys d'edat (0,64% i 0,79% pel 1990 i el 2010, respectivament). La fracció de la DMO en el total de la càrrega en salut regional augmentà en gairebé totes les regions del món.

4. A nivell mundial, el número de morts atribuïbles a la baixa DMO augmentà des de 103.000 pel 1990 a 188.000 pel 2010. Les morts atribuïbles a la baixa DMO gairebé es doblaren en homes des del 1990 (52.816) al 2010 (103.440), mentre que en dones l'increment fou d'aproximadament un 60% entre el 1990 (50.455) i el 2010 (84.146).

5. A nivell mundial, el número de DALYs atribuïbles a la baixa DMO augmentà des de 3.125.000 pel 1990 a 5.216.000 pel 2010. Àsia est i Àsia sud foren les regions que més contribuïren a l'increment de la càrrega mundial en salut de la baixa DMO. Les tasses de DALYs mundials per 100.000 habitants augmentaren significativament des del 1990 al 2010, però l'augment fou més discret amb l'estandardització per edat, la qual cosa reflecteix el creixement i

envelliment de la població. Les tasses estandarditzades per edat foren més altes, en general, en regions en vies de desenvolupament o subdesenvolupades. La mortalitat prematura (YLLs) contribuí a la càrrega mundial en salut lleugerament més que la discapacitat (YLDs), representant el 51% i el 53% de tots els DALYs atribuïbles a la baixa DMO pel 1990 i pel 2010, respectivament. Els homes obtingueren més DALYs que les dones tant pel 1990 com pel 2010, amb un 56% i un 60% de tots els DALYs pel 1990 i el 2010, respectivament.

6. La càrrega relativa en salut mundial de la DMO en comparació amb altres factors de risc en l'estudi GBD 2010 fou més aviat baixa. La classificació de la baixa DMO es trobà en la posició 20 entre 21 categories de factors de risc analitzats en les estimacions mundials pel 1990, i en la posició 23 entre 25 categories pel 2010. En general, la baixa DMO ocupà posicions més elevades en regions més desenvolupades. Una millora en la classificació mundial dels factors de risc s'observà en seleccionar els subgrups d'edat avançada, amb la posició màxima observada pel subgrup de població a partir de 70 anys d'edat, essent la baixa DMO l'11è factor de risc (d'entre 17 categories) amb el màxim nombre de DALYs al món pel 1990, i el 13è (entre 21 categories) pel 2010 (Figure 4.11) en aquest subgrup de població. Els resultats en les classificacions foren similar per homes i dones.

7 Projeccions de Futur

El projecte GBD és una iniciativa dinàmica. L'autora d'aquesta tesi forma part del grup de treball de l'estudi GBD 2013, el qual pretén actualitzar les dades obtingudes en la darrera versió del 2010. En aquest darrers projecte s'han tingut en compte moltes de les lliçons apreses exposades en aquesta tesi. Les millores en l'estimació de l'impacte en salut de la DMO inclouen:

1) Incorporació de noves dades epidemiològiques actualitzant la revisió sistemàtica; aquest cop també incloent individus entre els 20 i els 50 anys d'edat.

2) Actualització dels valors de referència pel llindar de DMO ideal en l'anàlisi de risc comparatiu (TMRED) amb fonts més recent de l'estudi NHANES.

3) Inclusió de tot tipus de lesions que tinguin com a conseqüència una fractura independentment de la causa (incloent, per tant, fractures resultant d'accidents de trànsit, assalts, etc).

4) La cerca de dades epidemiològiques fiables sobre la relació de risc entre DMO i fractura en poblacions joves. De moment, però, a data de presentació d'aquesta tesi, encara no s'han identificat estudis prospectius en població jove que abastin grans rangs d'edat, ja que les disponibles inclouen com a molt, dones premenopàusiques dels 40 als 50 anys d'edat.

5) La consideració d'incloure fractures diferents a les de maluc i vèrtebra en els càlculs de mortalitat deguts a baixa DMO. Aquest aspecte també es troba en

discussió actualment, ja que la informació en mortalitat continua estant basada en registres vitals i dades hospitalàries, i per tant, amb poca capacitat de detectar causes subjacents molt allunyades temporalment de l'esdeveniment de la fractura.

Per ajudar en tasques futures, és important que els sistemes d'informació en salut, així com els professionals que els utilitzen, estiguin preparats per detectar la mortalitat i la discapacitat a curt i llarg termini relacionades amb les fractures osteoporòtiques o amb totes aquelles fractures on l'osteoporosi hi juga un paper rellevant. En aquest sentit, augmentar la utilització dels codis relacionats amb l'osteoporosi, i la doble codificació (causa i naturalesa) de les lesions en els sistemes ICD és fonamental. La informació obtinguda pot ser utilitzada per les autoritats per una millor planificació en els programes de prevenció i maneig de l'osteoporosi.

L'equip d'investigadors principals en el MSK EG per l'estudi GBD 2010 es troba actualment col·laborant amb l'OMS (WHO) per tal que les malalties musculoesquelètiques, entre elles l'osteoporosi i les fractures per fragilitat, es trobin entre les prioritats marcades per l'OMS per les malalties no comunicables, i es reconegui mundialment el seu gran impacte en salut, especialment en termes de discapacitat.

THE GLOBAL BURDEN ATTRIBUTABLE TO LOW BONE MINERAL DENSITY

Original Thesis in English of Lídia Sànchez-Riera for presentation for the title of Doctor of Medicine

Table of Contents

Abstract

Introduction: Osteoporosis and osteoporotic fractures represent an enormous health burden and economic cost for most societies in the world, and future projections forecast their steady increase over the next few decades. Strategies to detect and treat those individuals with high risk of fracture have proved to be cost-effective, but still an important lack of awareness exists among health professionals, public health institutions and general population. Low bone mineral density (BMD) is one of the factors better correlated with fracture risk, and its predictive value for hip and non-hip fractures has been well established. Standard and easy methods to measure BMD are available, which allow to compare values among different population groups. The Global Burden of Disease Study 2010 estimated the worldwide health burden of 291 diseases and injuries and 67 risk factors. The main metrics for the burden measurements were the Disability-Adjusted Life Years (DALYs), the Years lived with disability (YLDs), the Years of Life Lost due to premature mortality (YLLs) and Deaths. For the first time, BMD was analysed as a risk factor for fractures, which formed part of the health burden due to falls. Risk analysis followed the Comparative Risk Assessment (CRA) methodology to determine which proportion of the falls burden was attributable to low BMD.

Objectives: To calculate the global distribution of BMD, its population attributable fraction (PAF) for falls, and the number of DALYs, YLDs, YLLs and deaths due to low BMD, with estimates for each region, age group, sex and time period (1990 and 2010).

Methods: Systematic review was performed seeking population-based studies with BMD measured by Dual-X-Ray-Absorptiometry at femoral neck in people 50 years and over. Age- and sex- specific levels of mean BMD+/-SD (g/cm2) were extracted from eligible studies. For the CRA methodology to calculate PAFs of BMD for fractures, the theoretical minimum risk factor exposure distribution was estimated as the age and sex-specific 90th percentile from NHANES III. Relative risks for fractures were obtained from a previous meta-analysis. Hospital data with double coding (cause and nature of injury) was used to calculate the fraction of the health burden of falls due to fractures.

Results: Global deaths and DALYs attributable to low BMD increased from 103,000 and 3,125,000 in 1990 to 188,000 and 5,216,000 in 2010 respectively. The contribution to the total DALYs was slightly superior for YLLs compared to YLDs. The percentage of low BMD in the total global burden almost doubled from 1990 (0.12%) to 2010 (0.21%). In population 70 years old and over these percentages increased from 0.64% in 1990 to 0.79% in 2010. Around one third of all falls-related deaths were attributable to low BMD. Males showed more contribution to the global deaths and DALYs, with a higher increase over time, compared to females. Low BMD was not among the top risk factors causing health burden in the world, although its relative weight was more important in older ages.

Conclusion: This is the first study of its kind in assessing the role of low BMD in the global health burden as a continuous variable. Results showed an increase of the burden worldwide, greatly influenced by the ageing of the population. A significant

fraction of all falls-related deaths and health burden in the world was attributable to low BMD and, therefore, preventable. Data systems should improve in the detection of injuries potentially related to low BMD and osteoporosis in general. This information can be used by health institutions and authorities to identify priorities and allocate resources.

Abbreviations

BMD	Bone mineral density
BMI	Body Mass Index
CI	Confidence Interval
CRA	Comparative Risk Assessment
CRFs	Clinical Risk Factors
CT	Core Team (refers to the Core Team of the GBD 2010 Study in the University of Washington)
CTX	Carboxy-terminal collagen crosslinks
CV	Coefficient of variation
DALY	Disability-Adjusted Life Year
DisMod-MR	Disease Modelling Meta-Regression Tool
DXA	Dual-x-ray-absorptiometry (also known as *DEXA*: dual-energy-X-ray-absorptiometry)
DW	Disability Weight
EG	Expert Group
ELG	Expert Leaders Group (for the Osteoporosis Working Group in the GBD 2010 study)
EMA	European Medicines Agency
EPOS	The European Prospective Osteoporosis Study
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
FN	Femoral Neck
FNBMD	Femoral Neck Bone Mineral Density
FRAX	WHO Fracture Risk Assessment Tool
Garvan	Garvan Fracture Risk Calculator
GBD	Global Burden of Diseases
GDP	Gross domestic product
GR	Gradient of risk (RR/SD)
HRpQCT	High resolution peripheral quantitative computed tomography
HRT	Hormone replacement therapy

ICD	International Statistical Classification of Diseases and Related Health Problems
IEG	Injury Expert Group
IHME	Institute for Health Metrics and Evaluation
IOF	International Osteoporosis Foundation
ISCD	International Society of Clinical Densitometry
LSC	Least significance change
MA	Meta-analysis
MSK	Musculoskeletal
MPO	Main project officer
NHANES	National Health and Nutritional Examination Survey
ORAI	Osteoporosis Risk Assessment Instrument
OST	Osteoporosis Self-assessment Tool
OSTA	Osteoporosis Self-Assessment Tool for Asians
OWG	Osteoporosis Work Group
P1NP	N-terminal extension peptide
PA	Physical Activity
PAF	Population attributable fraction
pDXA	Peripheral DXA
PE	Precision Error
pQCT	Peripheral Quantitative Computed Tomography
PTH	Parathyroid hormone
QALY	Quality-adjusted life years
QCT	Quantitative Computed Tomography
QUADAS	Quality Assessment Tool for Diagnostic Accuracy Studies
QUS	Quantitative Ultrasound
RoB	Risk of bias tool
RR	Relative Risk
RT	The Review Team
SCORE	Simple Calculated Risk Estimation Score
SD	Standard deviation
sBMD	Standardized Bone Mineral Density

sFNBMD	Standardized Bone Mineral Density at Femoral Neck
SR	Systematic review
SWAN	Study of Women's Health Across the Nation
TBS	Trabecular Bone Score
TMRED	Theoretical-minimum-risk exposure distribution
USD	The United States Dollar
VFA	Vertebral fracture assessment
WHO	World Health Organization
YLDs	Years Lived with Disability
YLLs	Years of Life Lost due to premature mortality

Justification of This Thesis. Professional and General Motivations

Since I was a medical student, I had always felt very attracted to travel abroad, and explore other ways to study and practice Medicine. My first overseas medical experience arrived as a medical student, when I enjoyed a scholarship of my local university in Reus, Tarragona, to attend the Queen's Medical Hospital in Nottingham, United Kingdom, as a visiting student during my last bachelor course. Later on, in the last year of my Rheumatology training in *Hospital Universitari de Bellvitge*, I was lucky enough to have a department's chief who was enthusiastic about student exchange and external rotations. I will never forget that Friday afternoon, when I appeared with the greatest disappointment in Joan Miquel Nolla's office, after receiving the letter from a San Francisco's institution (the name of which I would prefer to keep private) declining to accept any visiting fellows by free. Joan Miquel showed himself very supportive and sympathetic. We started to discuss other options, and suddenly he thought about Philip Sambrook and his Institute of Bone and Joint Research (IBJR) in Sydney University. The department of Rheumatology in Bellvitge had a long experience in Osteoporosis research, and professor Sambrook was one of the international figures in the field most admired by professor Nolla and the other team members. To be honest, I had never heard about that name before, and my clinical interest for bone metabolism diseases was rather low compared to inflammatory arthropathies. Then, Joan Miquel googled professor Sambrook and we went through his brief biography, his citations in Pubmed, and finally visited the IBJR and the University of Sydney websites, while we were both getting progressively more and more excited about the idea. In case I had any doubt regarding the suitability of the institution and the research team, Joan Miquel searched for some

nice photos of Sydney, including its glamorous beaches and its multinational cultural background. “The city of Nemo, you will love it and they will love you”, he said. I didn’t’ know who Nemo was, to what Joan Miquel answered “that is because you don’t have children”. I must say that I watched the movie “Finding Nemo” some years later, and my skin got goose bumps when I saw in the screen the cartoon skyline of Sydney. Once I was convinced that an external rotation in the IBJR could be a nice academic and life experience, we sent an email to Philip Sambrook, and to another professor of the same institution who seemed to be very active in the research of musculoskeletal diseases, Lyn March.

And this is how my research career begun. Lyn March answered our email on behalf of herself and the IBJR accepting my attendance as a visiting research fellow. So I spent a three-month period in this institution led by Philip Sambrook in 2007. During my stay, I took part in the *FREEDOM STUDY: A randomized controlled trial of sunlight and calcium supplementation to reduce vitamin D deficiency in older people in residential care*. Duties included data collection from the study subjects with the research team, preparation of blood samples in the laboratory, attendance to the study research meetings and manuscript writing. Besides, I attended some of the daily clinical and academic activities in the hospital as well as the meetings of the regional society of Rheumatology. Those three months completely changed the course of my career and my life in general. On one side, I had the privilege of working in an internationally recognized research institution, beside professionals of the greatest academic and human quality, who were generous enough to invest their time and energy in introducing me in the world of the formal medical research.

Working in the IBJR and participating in the FREEDOM study opened my eyes to the research in musculoskeletal diseases. I discovered how challenging was to investigate common conditions such as vitamin D deficiency, osteoporosis, osteoarthritis, and frailty in the elderly. Suddenly I realized what an enormous impact can have the study of such conditions in the overall population, and I decided I wanted to become part of the global network that works to improve the knowledge and management of common musculoskeletal conditions. It was not anymore about the study of rheumatic conditions; it was about public health and improving the health of the people at a population level…to make a difference! On the other side, I spent one of the most beautiful times in my life. Lyn March turned out to be the most extraordinary person I have ever met, admirable for her professional and personal achievements. Apart from her duties as Rheumatology consultant, professor of Public Health in the Medical School at the University of Sydney, and president of the Australian Society of Rheumatology at that time, she managed to have a lovely family and an endless list of good friends. She is one of those persons that radiates positivity around her. Lyn opened the doors of her knowledge and her house to me. So I fell in love with the IBJR, with medical research, with the March-Williams family, with the city of Sydney, with the Australian culture…and most importantly, I fell in love with Nicholas, a clinical researcher who is nowadays my best professional colleague, my husband and the father of the baby to come.

My stay in the IBJR in Australia in 2007 was awarded by The Catalan Society of Rheumatology (*Societat Catalana de Reumatologia*) and the Spanish Society of Rheumatology (*Sociedad Española de Reumatología*) with seldom prizes for short

overseas research stays. Overall, the experience could not have been better. At my return to Barcelona to finish the last year of my Rheumatology training, it was already clear I would be back to Sydney.

I worked in the Rheumatology department in *Hospital Universitari de Bellvitge* and *Hospital Sant Camil* for the following year*,* combining the clinics with research in premenopausal osteoporosis, led by Joan Miquel Nolla. Work was satisfying and life was nice; however, my internal will to go back to Australia was unstoppable. So when Lyn March contacted me in 2008 to go back to the IJBR and Sydney University as a visiting research fellow, I had no doubt about it. The purpose was to become the main project officer for Osteoporosis in an international epidemiological initiative called the Global Burden of Diseases (GBD) Study 2005 (changed to 2010 later on). The project was the greatest effort in Epidemiology ever done to update and improve estimations of the health burden for the main diseases, injuries and risk factors in the world. Lyn had been designated the leader of the Musculoskeletal Expert Group, which would be based in the University of Sydney. It was a great opportunity for a PhD project, with the only inconvenient that it was an honorary position and it could not be done fully funded through the University of Sydney. Joan Miquel, again, was very supportive and encouraging; we planned to undertake the project with the academic support from *Investigació Biomèdica de Bellvitge* (IDIBELL) and the *Universitat de Barcelona.* Lyn found the way to get funds for me through my participation in another research project, an international initiative led by the Outcomes Measures in Rheumatology (OMERACT) and the Osteoarthritis Research Society International (OARSI) about pain and functional disability in patients with

knee and hip osteoarthritis. This project represented around 30% of my research activity during my first two years in the GBD project, and in actual fact, turned out to be a great learning experience in terms of research logistics and international networking. Furthermore, it became my master's research project for *Universitat de Barcelona* when I undertook the *Màster en Investigació en Ciències Clíniques* as the first step for my PhD curriculum. Later on, with Joan Miquel and Lyn's support (as well as Loreto Carmona's), I successfully applied for the national grant from *Sociedad Española de Reumatología* for long overseas research stays in 2009 and 2010, which was only granted for two fellows per year and represented a great financial support at the time of a significant personal achievement.

My work in the GBD 2010 study was a challenging task. Since the end of 2008, I have dedicated an enormous amount of time to this project, with the main core papers published not before end 2012 and the musculoskeletal series just in 2014. Actually, "all" the musculoskeletal expert team has undertaken an amazing task, starting by their leaders Lyn March and Anthony Woolf. We used to joke with Lyn and talked about the "never-end study". However, the scientific and technical knowledge I have acquired is priceless, not to mention the great value of improving my English to the level of doing my things-to-do list in English. I can say that I finally achieved my goal of being part of the international network of professionals that work for a world where musculoskeletal conditions, particularly osteoporosis, are recognized in their burden for the people and the societies. I am still actively collaborating with the Institute for Health Metrics and Evaluations (University of Washington) and the World Health Organization in such goals. Recently, I have

started my work as an academic fellow in the University of Zurich, as part of an international leading research team in vitamin D deficiency, fractures and frailty in the elderly, led by Professor Heike Bischoff-Ferrari. When I look at all the things I have learned with this experience and all the extraordinary people coming to take part of my life, I can't regret any step I took.

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1 INTRODUCTION

1.1 Osteoporosis and Osteoporotic Fractures: Definition

Osteoporosis is defined as a systemic skeletal disease characterized by a low bone mass and a microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture (NIH Consensus Development Panel on Osteoporosis Prevention 2001). It behaves as a silent disease. A high percentage of affected people are not aware that they have the condition. Consequently, osteoporosis burden is better assessed by measuring the burden of its clinical outcome, i.e. osteoporotic fractures (also known as “”fragility fractures”), which usually occur after a low energy trauma, such as a casual fall. The most common and better characterized fractures are, by order of their disability burden, hip, vertebra, and wrist fractures. There are other peripheral fractures considered to be related to osteoporosis, such as proximal humerus, pelvis, rib, proximal tibia, clavicle, hand and foot fractures (Seeley, Browner et al. 1991).

For the last two decades, the operational definition for osteoporosis has been based on BMD values: osteoporosis may be diagnosed in postmenopausal women and in men age 50 and older if the BMD measured by dual-x-ray absorptiometry (DXA) at lumbar spine, total hip, or femoral neck (in certain circumstances the 33% distal radius may be utilized) is -2.5 standard deviations (SD) or less from the mean BMD value in young females (T score -2.5 or less) (WHO 1994; Kanis 2008) (Figure 1.1). The young reference values should be obtained by population-based studies and T scores should be calculated within the reference population, as BMD shows great geographical variation at population level (Sanchez-Riera, Wilson et al. 2010). Osteoporosis is less common in premenopausal women and younger men and

screening of secondary causes of osteoporosis (i.e. underlying health problems predisposing to the condition) needs to be thorough, as they account for a significant proportion of all the cases of osteoporosis in this subpopulation (Khosla, Lufkin et al. 1994). Based on BMD values from DXA, premenopausal women and men below 50 may be considered to be “below the expected range for age” when the BMD is -2.0 SD or less compared to the mean BMD of the age- and sex-matched peers (referred as the Z score) from the reference population. Diagnosis of osteoporosis in these population may be defined by the presence of a fragility fracture or a Z score -2.0 or lower in the presence of risk factors for osteoporosis (Binkley, Bilezikian et al. 2006; Watts, Leslie et al. 2013).

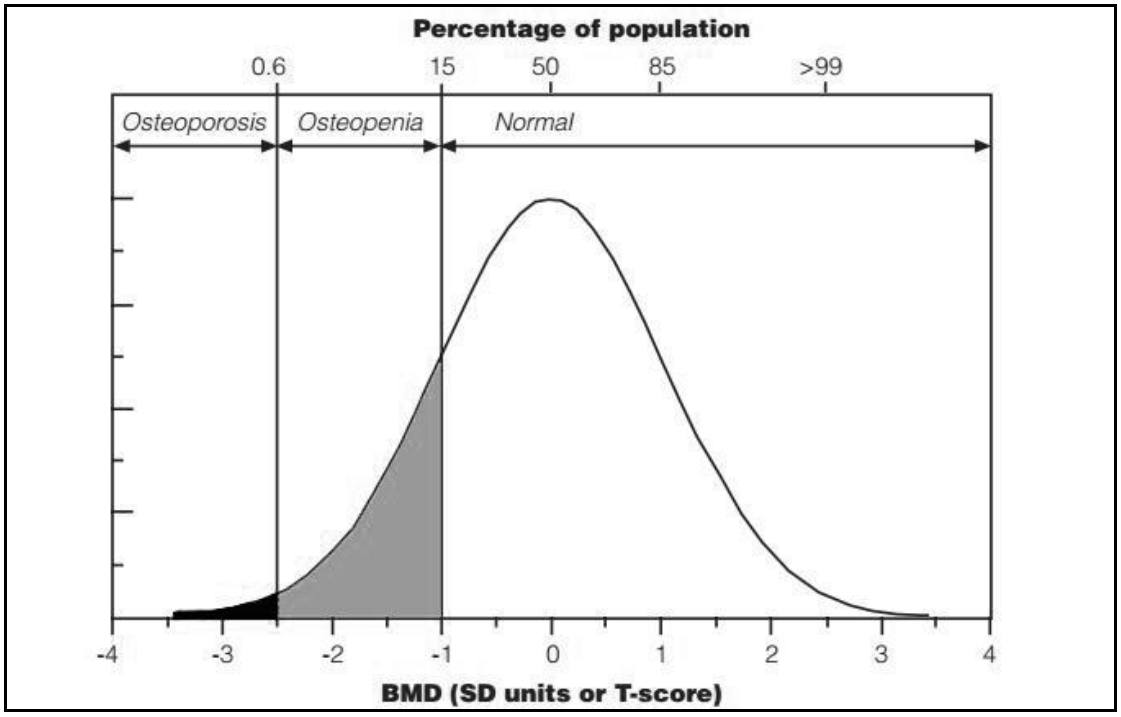

Figure 1.1 Classification Criteria by the World Health Organization (WHO)

T score represents the number of SD below the mean value of bone mineral density of the young female reference, which follows a normal distribution. Z scores are based in the same concept, although the Gaussian curve is within a specific sex and age group. BMD: bone mineral density. Adapted from World Health Organization (WHO 1994).

For clinical applications, T scores at the spine and Z scores are preferred to be country-specific, while an international reference has been purposed by world expert leaders (Kanis, McCloskey et al. 2008), and supported by the International Osteoporosis Foundation (IOF) (Kanis and Gluer 2000) and the International Society for Clinical Densitometry (ISCD) (Binkley, Bilezikian et al. 2006; Watts, Leslie et al. 2013) to define T scores based on femoral neck (FN) measurements. This approach

uses the mean BMD values at femoral neck (FNBMD) from the white young females at the National Health and Nutritional Examination Survey III (NHANES III) (Looker, Wahner et al. 1998), considered to be a truly population-based sample. It has the advantages of giving a single location for osteoporosis definition (i.e. FN), for both men and women, as well as enabling the application of a fracture prediction tool (i.e. FRAX®[®]) based on the most solid epidemiological data available to the moment in regards to the gradient of risk for fracture due to BMD (Johnell, Kanis et al. 2005). Moreover, it has the capacity to enable comparisons among different countries, therefore appearing suitable for epidemiological research.

The above definitions for osteoporosis are pragmatic for diagnostic and therapeutic decisions. However, based on such definitions, there is no burden associated with osteoporosis *per se* and it becomes difficult to have a real prevalence of the condition in a given population. Furthermore, the sensitivity of the BMD measures to predict an osteoporotic fracture is good but limited, as we will discuss later in this introduction (see *bone mineral density as a risk factor for osteoporotic fractures*). Despite its importance, BMD is not the only factor contributing to fracture susceptibility, and the latter is better predicted when other factors are taken into account. For this reason, the epidemiology of osteoporosis is better reflected by studying the epidemiology of osteoporotic fractures. Life-time risks and 10-year probability for fractures are more suitable to measure the burden of osteoporosis, and both the World Health Organization (WHO) and the IOF, a WHO-collaborating centre for metabolic bone diseases, have recommended the 10-year time frame to

base public health analysis and intervention thresholds (Genant, Cooper et al. 1999; Kanis and Gluer 2000).

1.2 Health Burden Related to Osteoporotic Fractures

Population-based studies in different world regions have found an independent relationship between low BMD at different skeletal sites and mortality (Trivedi and Khaw 2001; Pinheiro, Castro et al. 2006; Nguyen, Center et al. 2007; Bliuc, Nguyen et al. 2009; Suzuki and Yoshida 2009; Johansson, McCloskey et al. 2010). However, as mentioned previously, the health burden related to osteoporosis is better measured by accounting for the burden related to osteoporotic fractures, the consequences of which can range from chronic pain, loss of mobility and independence to institutionalization and death (Johnell and Kanis 2004; Johnell and Kanis 2006; Bliuc, Nguyen et al. 2009; Bertram, Norman et al. 2011).

Hip is the location of fracture where the health outcomes are potentially worst, partly because the peak incidence of such fractures occur in population 70-79 years old (Johnell and Kanis 2004), and therefore incidence is considerably higher in developed countries (Johnell and Kanis 2004). At 1 year after the hip fracture event, cumulative mortality reaches up to 37% in men and 25% in women and it is remarkably higher than in general population (Kanis, Oden et al. 2003; Kannegaard, van der Mark et al. 2010). Mortality is higher in men, even after adjusting by age and comorbidities (Kannegaard, van der Mark et al. 2010). About half of the patients lose their prior level of physical function and many lose their independence and require long-term care (Magaziner, Simonsick et al. 1990; Sernbo and Johnell 1993; Melton

2003). Only half of the survivors will walk again and often not at the same level as prior to the fracture (Magaziner, Simonsick et al. 1990; Sernbo and Johnell 1993; Melton 2003), and a high percentage report chronic pain after one year post-fracture (Bertram, Norman et al. 2011).

Vertebral fractures cause pain and limitation of the spinal movement, affecting considerably the overall quality of life (Naves Diaz, Diaz Lopez et al. 2001). Both prevalent and incident fractures increase steadily with age from 50 to 80 years of age (O'Neill, Felsenberg et al. 1996; Jansson, Blomqvist et al. 2010). One fifth requires hospitalisation and some will require subsequent long-term care (Silverman 1992; Ross 1997). Pain and disability become worse with each new fracture, as does the risk of mortality. Fractures occur more often in the thoracolumbar transition; spinal mobility is impaired even in the absence of significant pain. Despite only one third of the vertebral fractures being symptomatic (Cooper, Atkinson et al. 1992), undiagnosed vertebral fractures are also associated with disability (Silverman 1992; Ross 1997). Co-morbidity is common, such as kyphosis, restrictive lung disease and spinal stenosis, in particular at advanced ages, and contributes to the burden on quality of life and increased mortality (Kado, Browner et al. 1999). In a large prospective study in United States, women with one or more vertebral fractures showed 23% greater age-adjusted mortality rate, and this rate doubled in women with 5 or more vertebral fractures (Kado, Browner et al. 1999). Similar results were drawn from a longitudinal study in Sweden, where 28% of all deaths associated with vertebral fracture requiring hospital admission could be attributable to the fracture itself (Kanis, Oden et al. 2004).

Forearm fractures tend to occur in earlier ages than hip and vertebral locations with a peak incidence in women between 40 and 65 years old. Around one fifth of Colles' fractures (fractures of the distal radius with dorsal radius displacement, with or without ulna fracture) in developed countries result in hospitalisation (O'Neill, Cooper et al. 2001), which is often very prolonged in elderly patients (Lubbeke, Stern et al. 2005). Only 50% report a good functional outcome at 6 months (Kaukonen, Karaharju et al. 1988).

Premature death in the first year after a fracture, particularly at the hip site, is closely related to the short-term outcomes of the fracture (Cooper, Atkinson et al. 1993; Leibson, Tosteson et al. 2002; Ioannidis, Papaioannou et al. 2009), including the risks associated with prolonged hospitalisation and those related to the surgical repair or joint replacement that most of individuals require (except for vertebral fractures that more often don't require surgical intervention). Nevertheless, the excess risk for premature mortality after an osteoporotic fracture remains high for many years. Recent population-based studies with long follow up periods have estimated that mortality rates remain significantly higher than in the general population up to 5-15 years after the fracture event, and that includes not only hip fractures, but also most of the other sites for osteoporotic fractures (vertebral, pelvis, distal femur, proximal tibia, proximal humerus, multiple ribs) (Bliuc, Nguyen et al. 2009; Melton, Achenbach et al. 2013). For all ages, mortality following a fracture is higher in men than in women, particularly within the first year after the fracture, albeit the difference between mortality rates in both sexes tends to disappear over time (Melton, Achenbach et al. 2013).

1.3 Epidemiology of Osteoporosis and Osteoporotic Fractures

Osteoporosis has been estimated to affect 200 million women worldwide (Kanis 2007). For a person over 50 years living in a developed country, the lifetime risk of sustaining any fracture has been estimated in approximately 50% for women and 20% for men, most of these related to osteoporosis (Sanders, Nicholson et al. 1999; van Staa, Dennison et al. 2001). Considering the ageing of the global population, the worldwide incidence of hip fracture is projected to increase by three-fold by 2050 compared to 1990 (Gullberg, Johnell et al. 1997).

Epidemiology of osteoporosis was recently gathered from 58 countries around the world from an important systematic review on hip fracture incidence (Oden, McCloskey et al. 2013). Prevalence of osteoporosis defined by T score of -2.5 or less using international reference standard (white 20-29 females from NHANES III), was around 3% and 10 % in men and women 50-59 years of age, respectively. This percentage increased to 6% and 19% respectively in population aged 60-69, followed by 9% and 35% respectively in those aged 70-79, and finally, 19% and 51% respectively in people aged 80 or over. The countries included in such study accounted for around four fifths of the world population aged 50 years or more. Extrapolating the data to the world, the authors estimated that approximately 2.7 million hip fractures took place in 2010, of which approximately half were attributable to osteoporosis (264,000 for men and 1.10 million for women), and therefore potentially preventable.

Previous works from the global burden of diseases (GBD) initiative estimated 9.0 million osteoporotic fractures in the world in the year 2000, of which 1.6 million were at the hip (70% women), 1.7 million were at the forearm (80% women) and 1.4 million were clinical vertebral fractures (58% women) (Johnell and Kanis 2006). Although hip fractures only accounted for 18.2% of all fractures, they represented 40% of all the global health burden due to fractures, reflecting the higher mortality and disability of hip fractures compared to other sites.

The greatest number of fractures was in Europe, followed by the Western Pacific region, Southeast Asia and the Americas. Collectively, these regions accounted for the 97% of the overall numbers of fractures worldwide, highlighting the influence of the aging populations on the incidence of osteoporotic fractures, in particular on hip fracture rate, with a peak number between 75 and 79 years for both men and women (Johnell and Kanis 2006). When combining mortality and disability in the same standard measure, known as disability-adjusted life years (DALYs), osteoporotic fractures accounted for more DALYs lost than rheumatoid arthritis and all sites of cancer, with the exception of lung cancer (Johnell and Kanis 2006).

Life expectancy in North Africa and Middle East has improved significantly in the last two decades, with the consequent increased number of population at risk for fracture in such regions, becoming in some countries one of the top health priorities (International Osteoporosis Foundation 2011). In Sub-Saharan Africa, given the population structure with reduced life expectancy and high levels of mortality related to communicable diseases and nutritional deficiencies, osteoporosis and fragility

fractures are currently not a lead priority in the public health interventions in this region. Life expectancy is still considerably lower compared to developed countries, with an average of 56 years and only small percentage of the population being over 60 years of age. However, studies in this region show the same paradigm of increased fracture risk with age (Zebaze and Seeman 2003).

1.3.1 Geographic variation

One important fact is that fracture incidence is country-specific (Kanis, Johnell et al. 2002); variations between countries can be as high as a 15-fold range in the 10-year probability of hip fracture between Norway and Chile or Korea (Kanis, Johnell et al. 2002) (Table 1.1). This observation outlines the limited weight of the life expectancy and the BMD to explain the important differences between countries, given the variations in life expectancy and BMD are much less than variations in risk of hip fracture (Kanis, Johnell et al. 2002). A clear example of this is the lower risk of fracture in Southern countries in Western Europe compared to Northern countries, despite BMD levels being higher in the latter (Kanis, Johnell et al. 2002) (Table 1.1). One major longitudinal study showed that differences in falls incidence across countries could play a major role in such geographical variation (Roy, Pye et al. 2002). This probably reflects the role of other underlying factors such as diet, comorbidities, sunlight exposure, physical activity, and other cultural and environmental conditions.

A study done on Southern Chinese women in Hong Kong showed that the 10-year risk of osteoporotic fracture in 50–79 year of age was comparable to white women in

Spain, the United Kingdom, and Sweden, but was higher than that for a similar population in mainland China (Kung, Lee et al. 2007). Although women in mainland China have in average lower body mass index (BMI) and lower BMD than white Caucasian, the former show a lower risk of hip fracture, suggesting an important role of their shorter femoral neck and a more active lifestyle, which results in a lower risk of falling and a subsequent lower risk of hip fracture (Cummings, Cauley et al. 1994; Cummings, Xu et al. 1994). The effect of racial variations of the hip geometry has been claimed as well to explain the lower risk in hip fracture of Japanese American compared to white American, despite Japanese women show a lower mean BMD in FN (Nakamura, Turner et al. 1994).

Table 1.1 Ten-year probability of hip fracture averaged for age and gender and adjusted to the probabilities of Sweden (risk ratio of 10-year hip fracture for Sweden =1.00)

Europe		Non-Europe	
Country	Relative Probability	Country	Relative Probability
Norway	1.24	USA	0.78
Iceland	1.02	China (TW)	0.72
Denmark	0.85	Canada	0.65
Germany	0.72	Singapore	0.62
Switzerland	0.71	Kuwait	0.59
Finland	0.68	Australia	0.57
Greece	0.66	China (HK)	0.49
Netherlands	0.64	Japan	0.39

Hungary	0.63	Argentina	0.36
Italy	0.61	China	0.29
UK	0.60	Turkey	0.18
Portugal	0.57	Korea	0.18
France	0.41	Venezuela	0.17
Spain	0.39	Chile	0.08

Note that relative probabilities are expressed here without the 95% confidence intervals from the original source. TW: Taiwan, HK: Hong Kong.

Adapted from Kanis JA et al 2002 (Kanis, Johnell et al. 2002).

Marked geographical variation is also observed in population levels of BMD (Sanchez-Riera, Wilson et al. 2010). Ethnicity background, anthropometric variables and nutritional habits might account for a significant part of the observed worldwide differences, as shown in some studies where geographical differences in the BMD were related to such factors (Lunt, Felsenberg et al. 1997; Deleze, Cons-Molina et al. 2000).

In general, Asian ethnicity is related to lower BMD values compared to other ethnicities, even when adjusted by BMI (Goh, Low et al. 2004). Very low BMD values have been observed in Sub-Sahara region (Aspray, Prentice et al. 1996), where BMD was found to be lower in African black than in British white, although minimal trauma fractures are rare in the former. Black Americans and Brazilians by contrast, show higher BMD than white Americans, even after adjustment for socioeconomic level (Looker, Wahner et al. 1998; Siqueira, Facchini et al. 2005). Such variations

among black skin subjects from different world regions are probably partly explained by differences in nutrition and other environmental factors.

1.4 Economic Cost of Osteoporotic Fractures

The economic burden of osteoporosis results both from acute outcomes, such as hospital admission and surgery after an incident fracture, as well as long-term consequences related to chronic disability and costs of pharmacological and non-pharmacological interventions. Simultaneously, the costs are classified in *direct* (e.g. treatment of incident fractures, pharmacological prevention, institutionalization, etc), *indirect*, which basically correspond to the productivity losses, and *intangible*, referring to the monetary value of quality-adjusted life years (QALYs) lost. The term QALY refers to the number of years lived in "perfect health", and a year of life lived in a state of less than this perfect health is worth less than one. QALYs are often combined with costs to assess cost-effectivity of medical interventions (Hodgson and Meiners 1982).

In a recent review elaborated in collaboration with the IOF and the European Federation of Pharmaceutical Industry Associations, several aspects of the osteoporosis epidemiology in Europe were thoroughly reviewed (Hernlund, Svedbom et al. 2013; Strom, Borgstrom et al. 2013). The cost of osteoporosis, including pharmacological intervention in the EU in 2010 was estimated at €37 billion. Costs of treating incident fractures represented 66 % of this cost, pharmacological prevention 5 % and long-term fracture care 29 %. Excluding cost of pharmacological prevention, hip fractures represented 54 % of the costs, "other fractures" represented 39 %, and

vertebral and forearm fractures represented 5 % and 1 %, respectively (Hernlund, Svedbom et al. 2013). Costs derived from fragility fractures were estimated to be superior to some disorders with high disabling potential such as strokes, Parkinson and rheumatoid arthritis (Strom, Borgstrom et al. 2013).

Due to changes in population demography in Europe, there is an expected increment in the number of people affected with osteoporosis (using WHO diagnostic criteria) and in the annual number of fractures in the following years (estimated in 23 % and 28%, respectively, from 2010 to 2025). Because of this, the number of QALYs lost annually due to fractures have been predicted to increase from 1.2 million in 2010 to 1.4 million in 2025, corresponding to an increase of 20%. The total cost including values of QALYs lost (valued at 2 × Gross Domestic Product (GDP) per capita) in the EU would, then, rise from €98 billion in 2010 to €121 billion in 2025, corresponding to an increase of 22% (Hernlund, Svedbom et al. 2013).

The increasing incidence of fragility fractures over time has been likewise predicted for North America, Latin America, Australasia, Middle East-North Africa and Asia (Cooper, Campion et al. 1992; Gullberg, Johnell et al. 1997). The role of the fast demographics changes in high-populated word regions such as Latin America and Asia, with a substantial increasing trend in population levels of life expectancy, is shifting the global burden of osteoporosis towards such regions. By 2050, more than half of all hip fractures in the world are expected to occur in Asia (Cooper, Campion et al. 1992). As a paradigm of this, in China, the cost of hip fracture has been increasing at a rate of 6% per year. In 2006, the country spent around 1.5 billion

USD treating hip fracture and it is been estimated that this will rise to 12.5 billion USD in 2020 and by 2050 to more than 264.7 billion USD (Wang, Tao et al. 2009).

To understand the magnitude of the problem in Western societies is helpful to compare with other common diseases. In Sweden, for example, the annual cost resulting from major osteoporotic fractures (hip, vertebral and wrist) was estimated to be very close to that resulting from diabetes and to account for about 3% of the total health care cost in Sweden (Borgström, Sobocki et al. 2007). The greatest annual costs resulted from the acute care (58%) and community care (38%), with hip fractures being responsible of over three fourths (78%) of the total costs, followed by vertebral fractures (17%) and wrist fractures (5%). The economic impact of osteoporosis compared with other common conditions was also reflected by Swiss administrative data on women hospitalization. For the year 2000, incidence of hospitalization for osteoporosis or its complications was double than for breast cancer, myocardial infarction or stroke, three-times as high as that for chronic obstructive pulmonary disease, and six-times higher than that for diabetes (Lippuner, Golder et al. 2005) (Figure 1.2). The mean length of stay for osteoporosis was comparable to that of all the other diseases included in the analysis, except for stroke (twice as long) (Figure 1.3).

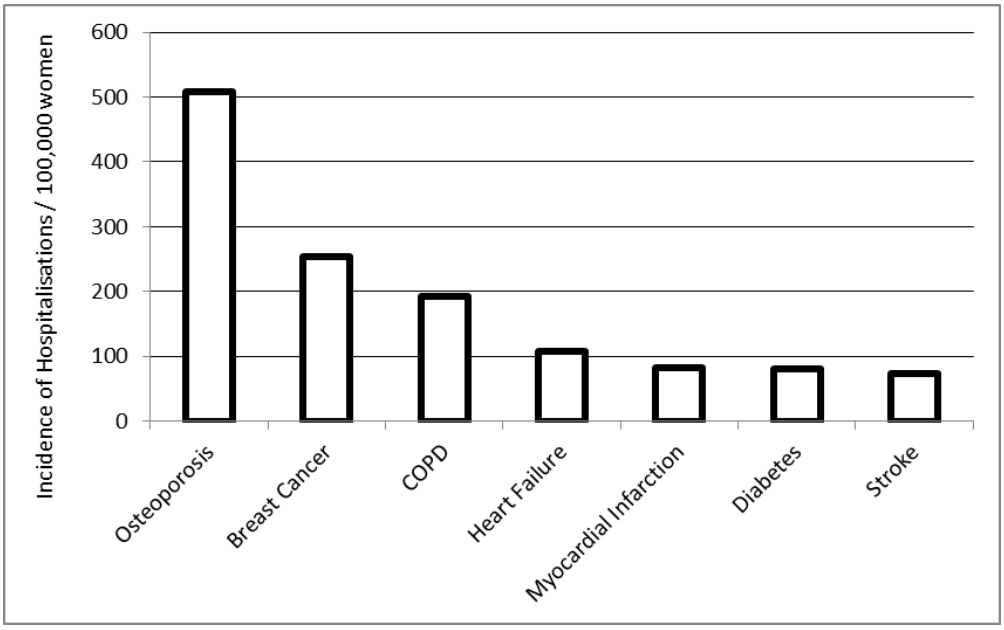

Figure 1.2. Incidences of hospitalization for osteoporosis and other frequent diseases in Swiss women in year 2000.

Adapted from Lippuner et al 2005(Lippuner, Golder et al. 2005).

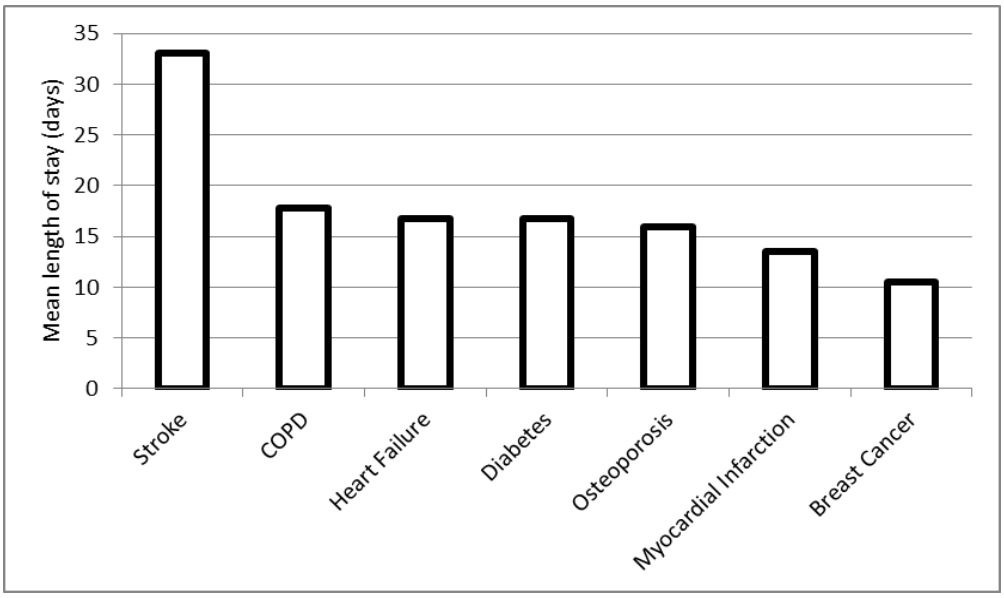

Figure 1.3 Mean length of stay for osteoporosis and other frequent diseases in Swiss women in year 2000.

Adapted from Lippuner et al 2005 (Lippuner, Golder et al. 2005).

1.5 Risk Factors for Osteoporosis and Fractures. Role of Bone Mineral Density and Importance of Clinical Risk Factors

1.5.1 Bone mineral density as a risk factor for fractures

Bone strength primarily reflects the integration of BMD and bone quality. The latest may be cumbersome to assess on the individuals and more so at a population level. In contrast, BMD is a well-defined predictor of fracture risk (Marshall, Johnell et al. 1996; Johnell, Kanis et al. 2005), and can be easily measured with standard techniques that are objective, reproducible, non-invasive, fast and relatively inexpensive. Besides, BMD is potentially modifiable through a great variety of non-pharmacological (calcium intake, sunlight exposure, physical activity, smoking cessation, etc) and pharmacological interventions (please, refer to next chapter 1.6 Diagnosis and Management of Osteoporosis). Therefore, it provides an excellent scenario for the management and follow-up of the individuals at high risk of fracture.

Dual-x-ray-absorptiometry (DXA) at central sites (i.e. spine and hip) still stays as the most broadly used and validated technique to measure BMD, and is the recommended technique for both clinical management and research purposes (WHO 1994; The International Society for Clinical Densitometry 2007). Other techniques, like peripheral quantitative ultrasound (QUS), peripheral DXA (pDXA), spine and hip quantitative computed tomography (QCT) and peripheral QCT (pQCT) have shown a valid correlation with the fracture risk (Genant, Block et al. 1987; Marshall, Johnell et al. 1996; Johnell, Kanis et al. 2005; Moayyeri, Adams et al. 2012; Dennison, Jameson et al. 2014). The first two offer some advantages over the

classical central DXA due to their fast performance, low cost, and easy portability. Yet, due to the lack of enough normative data, the use of such techniques is generally limited to screening strategies in conjunction with clinical risk factors, particularly in situations with low access to classical central DXA (Internaional Society of Clinical Densitometry 2013) (Internaional Society of Clinical Densitometry 2013). High resolution peripheral QCT (HR-pQCT) offers good imaging on bone microarchitecture and quality, but high levels of radiation, limited accessibility and affordability are major concerns for its applicability at a population level. The above-mentioned WHO threshold of -2.5 SD of T score for osteoporosis definition using spine and hip BMD measured by classical densitometers (Kanis 2008) cannot be applied to any of the other forms of BMD measurement (except for DXA at distal radius, which can be particularly useful in some occasions when hip and spine sites are subjected to important artefacts, such as metallic surgical materials). More recently, trabecular bone score (TBS) from DXA image of the lumbar spine has been advocated as a potential tool to improve fracture prediction. While TBS is not a direct physical measurement of trabecular microarchitecture, it has been shown to be associated with trabecular microarchitecture and bone strength by HRpQCT. Moreover, cross-sectional and prospective studies, involving a large number of subjects, have both shown that TBS is associated with vertebral, femoral neck, and other types of osteoporotic fractures (Silva and Bilezikian 2014).

Nevertheless, the risk of fracture due to reduced BMD is gradual over a continuum, and in actual fact, most of osteoporotic fractures occur in patients with osteopenia (i.e. between 1 and 2.5 SD below mean BMD of young population) (Siris, Chen et al.

2004). Likewise, although less frequently, fractures can occur in subjects with normal BMD (T score above -1.0). Thus, the threshold to define osteoporosis by absorptiometry, somewhat arbitrary, has low sensitivity to detect individuals at high risk of fracture. As well pointed out previously (Oden, McCloskey et al. 2013), though, it is not more arbitrary than the threshold set for other important biological variables such as blood pressure for hypertension or BMI for obesity. Actually, the ability of hypertension and hypercholesterolemia to predict stroke and myocardial infarction, respectively, are not better than the predictive value of BMD for fractures (Marshall, Johnell et al. 1996).

The gradient of risk (GR) for fracture due to BMD has been defined as the relative risk (RR) for fracture for each unit (either SD in T score or absolute value of BMD measured in g/cm^2) of BMD decrease. An important meta-analysis on the relationship between BMD and fractures published in 1996 (Marshall, Johnell et al. 1996) found that measurements at any site (hip, spine and wrist) predicted any osteoporotic fracture with a GR of approximately 1.5 per SD decrease in BMD. Risk assessment was improved by site-specific measurements, so to predict hip fractures and vertebral fractures, accuracy was better when measurement was done in the hip or in the lumbar spine, respectively (Table 1.2). The highest gradient of risk was found at the hip to predict hip fracture where the gradient of risk was 2.6. This means that a subject with a T-score of −3 SD at the hip would have a 2.6^3 or about 17-fold higher risk than the same subject with a T-score of 0 SD. Almost 10 years later, a new meta-analysis based on 12 population-based studies from Western Europe, USA, Canada, Japan and Australia found similar values (Johnell, Kanis et al. 2005).

In this latest study, FNBMD was found to be a good predictor for hip fracture, for osteoporotic fracture and for any fracture; the GR increased slightly with age from 50 years to 85 years for any osteoporotic fracture, while the effect was the opposite when hip fractures were analysed alone. These finding may be a reflection of the higher frequency of additional clinical risk factors in the elderly population (poor bone quality, higher risk to falls), while in young population low BMD might be a stronger predictor of the overall fracture risk. Although fracture events occurred more often in women, the GR per FNBMD unit was equivalent for men and women, which means that the "excess" of fracture risk due solely to BMD is comparable between both sexes.

Table 1.2 Age-adjusted relative increase in risk of fracture (with 95% confidence interval) in women for every 1 SD decrease in bone mineral density measured by Dual-X-Ray-Absorptiometry below the mean value for age

Site of measurement	All Fractures	Forearm Fracture	Hip Fracture	Vertebral Fracture
Femoral Neck	1.6 (1.4-1.8)	1.4 (1.4-1.6)	2.6 (2.0-3.5)	1.8 (1.1-2.7)
Distal Radius	1.4 (1.3-1.6)	1.7 (1.4-2.0)	1.8 (1.4-2.2)	1.7 (1.4-2.1)
Lumbar Spine	1.5 (1.4-1.7)	1.5 (1.3-1.8)	1.6 (1.2-2.2)	2.3 (1.9-2.8)

Adapted from Marshall et al 1996 (Marshall, Johnell et al. 1996).

1.5.2 Importance of clinical risk factors for fractures

The predictive value of BMD to assess fracture risk can be improved with the input of other independent clinical risk factors (Kanis, Oden et al. 2007). Risk assessment tools exist in order to estimate the fracture risk of an individual even in the absence of a BMD testing. A systematic review published in 2013 found 48 fracture risk predicting tools, of which 20 had been externally validated (Rubin, Friis-Holmberg et al. 2013). Of those, authors found that only 6 had been tested more than once in a population-based setting with acceptable methodological quality as assessed with the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) checklist (Hollingworth, Medina et al. 2006): Osteoporosis Self-assessment Tool (OST), Osteoporosis Risk Assessment Instrument (ORAI), Garvan Fracture Risk Calculator (Garvan), Simple Calculated Risk Estimation Score (SCORE), WHO Fracture Risk Assessment Tool (FRAX®), and Qfracture. Probably, the most widely used of such predictive tools is the FRAX®. The FRAX® model is a WHO initiative currently available for different countries on-line (http://www.shef.ac.uk/FRAX), and it is been developed through the analysis of twelve longitudinal population-based cohorts from North America, Europe, Asia and Australia (Johnell, Kanis et al. 2005). This index takes into consideration 12 risk factors apart from femoral neck BMD: age, sex, weight, height, previous history of fracture, smoking habit, glucocorticoid therapy, rheumatoid arthritis, secondary osteoporosis and alcohol intake (Table 1.3). The tool allows the calculation of 10-year probability of hip and any osteoporotic fracture at a country-specific level, even in the absence of BMD information. Interestingly, authors from the abovementioned review (Rubin, Friis-Holmberg et al. 2013) found that simple tools such as OST and Garvan often performed as well as the more complex

ones such as FRAX® and SCORE. Even more, a previous study done with an international cohort of almost 20,000 postmenopausal women found that FRAX® and Garvan tools were not superior in predicting fracture in the absence of BMD than a simple model using only age and history of prior fracture (Sambrook, Flahive et al. 2011).

Table 1.3 Risk factors for fracture included in the FRAX® tool

Different Risk Factors
Age
Sex
Low body Mass
Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
Parental history of hip fracture
History of fragility fracture
Glucocorticoid treatment (≥5mg oral prednisolone daily for 3 months or more)
Current smoking
Alcohol intake 3 or more units daily
Rheumatoid arthritis
Other secondary causes of osteoporosis - Untreated hypergonadism in men and women, e.g., premature menopause, bilateral oopherectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism - Inflammatory bowel disease, e.g., Crohn's disease and ulcerative colitis.

Different Risk Factors
- Prolonged immobility, e.g., spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis - Organ transplantation - Type I diabetes - Thyroid disorders, e.g. untreated hyperthyroidism, over-treated hypothyroidism - Chronic obstructive pulmonary disease

Adapted from Kanis et al 2008 (Kanis 2008).

The most relevant clinical risk factor related to suffering a fracture is age (Kanis, Johnell et al. 2001). It is been shown that the risk of fracture increases with age at any given T score and it does dramatically from 50 to 80 years of age at the same threshold of -2.5 SD (Kanis, Johnell et al. 2001). The effect of age on fracture risk independently of BMD is one of the most powerful reasons to suggest intervention thresholds not based on fixed T-scores, but according to absolute probabilities of fracture (Kanis, Johnell et al. 2001). From an epidemiological point of view, age is a key question as well when assessing the burden of osteoporosis, as we can predict that the burden will be higher in those world regions with a more aged population.

Gender is the second clinical risk factor that appears important in fracture risk: both osteoporosis and fractures are more common in women (Johnell and Kanis 2006; Oden, McCloskey et al. 2013). In 2000, of all the 9.0 million osteoporotic fractures estimated worldwide, 61% occurred in women; the percentage was 70% for hip

fractures, 80% for forearm fractures and 58% for vertebral fractures (Johnell and Kanis 2006). Reasons behind the female/male ratio predominance are diverse. First, physiological: women reach lower levels of peak bone mass at young ages, and higher bone loss rates as older adults compared to men due to estrogen deprivation after menopause (Berger, Goltzman et al. 2010). The lack of estrogens also involves a faster speed of deterioration of bone structure in females compared to males (Zhang, Tan et al. 2010), therefore compromising bone strength. Second, epidemiological: women have a higher life expectancy in most of the world regions (Wang, Dwyer-Lindgren et al. 2012). Finally, females exhibit an increased risk of falling compared to men (Winner, Morgan et al. 1989; Roy, Pye et al. 2002; Kayan, Johansson et al. 2009), yet in age-standardized falls rates (Roy, Pye et al. 2002), and it is well proven the role of falls as an independent predictor of fracture risk (Roy, Pye et al. 2002; Kayan, Johansson et al. 2009).

The history of a previous fracture event is one of the other major risk factors for fractures. One meta-analysis estimated that the risk of any fracture, any osteoporotic fracture and hip fracture doubled in population 50 years and over when a previous fracture history was present (Kanis, Johnell et al. 2004). Interestingly, the RR for fracture decreased little when adjusted by BMD. There was no significant difference in the RR between men and women. One of the population-based studies included in the aforementioned meta-analysis, reported that 30% of women and 22% of men with a prior history of a fracture experience a new fracture during the next 5 years (Bliuc, Nguyen et al. 2009). A 5-fold probability of new vertebral fracture has been observed during the first year after a vertebral fracture compared to non-fractured

patients (Lindsay, Silverman et al. 2001). A prior wrist fracture has shown to increase the risk of a future wrist fracture about 3-fold and doubled the risk of any osteoporotic fracture (Barrett-Connor, Sajjan et al. 2008).

The role of weight and BMI on BMD and fractures has been in like manner well established in different male and female populations around the world (Cauley, Fullman et al. 2005; De Laet, Kanis et al. 2005; Kaptoge, Reid et al. 2007; Beck, Petit et al. 2009; Kim, Oh et al. 2009; Orito, Kuroda et al. 2009; Genaro, Pereira et al. 2010; Langsetmo, Poliquin et al. 2010; Sheng, Xu et al. 2010). One meta-analysis showed that a BMI below 20 doubled the risk of hip fracture compared to a BMI of 25 and increased, though to a lesser extent, the risk for any other fracture (De Laet, Kanis et al. 2005). The effect of BMI on fracture risk is in great part dependant on its effect on BMD (the lower BMI, the lower BMD) (De Laet, Kanis et al. 2005). However, the relationship between BMI and fracture risk is not linear, as evidenced by obesity (BMI 30 and over) being a poor protector against fractures (De Laet, Kanis et al. 2005; Beck, Petit et al. 2009). In actual fact, recent investigations have demonstrated the positive effect of lean mass (in comparison to fat mass) on bone mass and strength, although these parameters don't appear suitable for fracture prediction models at the moment (Leslie, Orwoll et al. 2014).

Physical activity (PA) is a good predictor of BMD (Bonaiuti, Shea et al. 2002; Broussard and Magnus 2004; Devine, Dhaliwal et al. 2004; Morseth, Emaus et al. 2010) and fracture risk (Ensrud, Ewing et al. 2007; Cauley, Harrison et al. 2013; Cawthon, Blackwell et al. 2014; Feskanich, Flint et al. 2014), explained by different

mechanisms. On one side, exercise increases quantity and quality of trabecular and cortical bone, therefore increases bone strength and resistance (Cousins, Petit et al. 2010; Janz, Letuchy et al. 2014). On the other side, exercise also improves muscle strength, balance and gait, important components of the falls risk in the elderly. In fact, different physical function parameters (such as grip strength, balance and walking speed) have been related to a reduced fall risk both in community-dwelling (Nevitt, Cummings et al. 1991; Ensrud, Ewing et al. 2007; Cauley, Harrison et al. 2013) and institutionalized individuals (Wilson, Hilmer et al. 2011). The predictive value of PA for falls varies with age and the presence of other comorbidities. Albeit PA and participation in social activities could lead to an increased likelihood of fall, evidence shows that those elderly with poor physical performance are more prompted to suffer injurious falls than those showing better physical parameters (Nevitt, Cummings et al. 1991; Ensrud, Ewing et al. 2007; Cauley, Harrison et al. 2013).

Falls constitute one of the major risk factors for fractures in elderly population (Roy, Pye et al. 2002; Ensrud, Ewing et al. 2007; Deprey 2009), but their predictive value for fractures is very low: while the majority of osteoporotic fractures occur after a fall event, most of the falls in the community don't have a fracture as an outcome (Nevitt, Cummings et al. 1991; Roy, Pye et al. 2002). Despite clinicians need to take into account the PA levels and falls frequency when considering absolute fracture probability in a subject, such parameters have not been incorporated in the FRAX® algorithm yet, possibly due to the heterogeneity of the studies and the consequent difficulty in conducting a proper meta-analysis. Fracture prediction tools incorporating

falls frequency, such as Garvan, did not prove to be superior to more parsimonious models in postmenopausal women (Sambrook, Flahive et al. 2011). Fast and objective measurements of physical function, such as sit-to-stand test or grip strength might more adequate to use in the clinical practice when assessing fracture risk and prevention.

Other factors, such as smoking, alcohol intake, and several clinical conditions have been identified as independent risk factors for low bone mineral density and fractures (Table 1.3). Among pharmacological causes of secondary osteoporosis, glucocorticoid therapy has the highest prevalence and fracture burden, and often represents the leading cause of secondary osteoporosis in developed countries (Allport 2008; Civitelli and Ziambaras 2008). Other therapies that increase the incidence and/or prevalence of medication-induced osteoporosis and fracture include androgen-deprivation therapy, aromatase inhibitors, protease inhibitors, selective serotonin reuptake inhibitors and prolactin-raising antiepileptic agents (Allport 2008). In the past few years, efforts have been made to summarize and quantify the effect of such conditions on fracture risk (Kanis, Borgstrom et al. 2005; Kanis 2008; Kanis, Johansson et al. 2009) (Table 1.4).

Table 1.4. Risk Ratios for Osteoporotic Fracture Associated with Risk Factors for Age, with and without Adjustment for Bone Mineral Density.

Risk indicator	Without BMD	With BMD
Alcohol intake ≥3 units daily	1.38 (1.16-1.65)	1.36 (1.13-1.63)
BMI (20 v 25kg/m^2)	1.27 (1.16-1.38)	1.02 (0.92-1.13)
BMI (30 v 25kg/m^2)	0.89 (0.81-0.98)	0.96 (0.86-1.08)
Current smoking	1.29 (1.17-1.43)	1.13 (1.00-1.25)
Ever use of systemic corticosteroids	1.65 (1.42-1.90)	1.66 (1.42-1.92)
Parental history of hip fracture	1.54 (1.25-1.88)	1.54 (1.25-1.88)
Prior fracture after 50 years	1.86 (1.72-2.01)	1.76 (1.60-1.93)
Rheumatoid arthritis	1.65 (1.20-2.02)	1.47 (1.12-1.92)

Values are risk ratios followed by 95% confidence intervals in brackets. BMD: bone mineral density; BMI: body mass index. Adapted from Kanis et al 2009 (Kanis, Johansson et al. 2009).

In general, each risk factor on its own scores poor specificity and sensitivity in predicting fracture probability, and the influence on fracture risk (Table 1.4), as seen to occur with BMD, varies with age. Still the predictive value can be improved by combining different risk factors in the algorithm (Kanis 2008) (Table 1.5).

Table 1.5. Ten-year probability (%) of a major osteoporotic fracture (clinical spine, hip, forearm and humerus fracture) according to bone mineral density and the number of clinical risk factors for women aged 60 years in the UK.

Number	BMD T-Score at the Femoral Neck					
of CRFs	1.0	0.0	-1.0	-2.0	-3.0	-4.0
0	4.1	4.6	5.5	7.7	12	23
1	6.0 (3.9-8.4)	6.8 (4.5-9.5)	8.0 (5.5-11)	11 (8.2-14)	18 (15-21)	32 (29-37)
2	8.6 (4.6-14)	9.8 (5.4-16)	12 (6.7-18)	16 (10-24)	25 (19-34)	44 (38-54)
3	12 (5.9-22)	14 (6.9-25)	16 (8.7-28)	23 (14-36)	35 (25-49)	58 (48-68)
4	17 (9.4-28)	19 (11-31)	22 (14-35)	31 (22-44)	46 (35-59)	71 (59-78)

The range is not a confidence interval but, because the weight of different risk factors varies, is a true range. BMD: bone mineral density; CRF: clinical risk factor. Adapted from Kanis et al 2009 (Kanis, Johansson et al. 2009).

1.5.3 Role of vitamin D and calcium

Vitamin D deficiency leads to secondary hyperparathyroidism and has been found to be related to osteoporosis (Holick 2007), hip fractures (LeBoff, Kohlmeier et al. 1999; Bischoff-Ferrari, Can et al. 2008; Cauley, Parimi et al. 2009) and non-hip fractures (Nakamura, Saito et al. 2010). Osteomalacic changes, characterized by the accumulation of unmineralized matrix in the bone, can occur in the presence of persistent severe vitamin d deficiency, and have been found in a significant percentage of individuals sustaining a hip fracture (Harma, Parviainen et al. 1987; Arnala, Kyrola et al. 1997). A recent meta-analysis showed that doses of vitamin D over 800 IU daily were associated with a risk reduction of 30 % for hip fracture and

14% for any non-vertebral fracture (Bischoff-Ferrari, Willett et al. 2012). It is thought that the mechanisms behind such risk reduction are not only related to the positive effect on the bone mineralization, but also to the role of vitamin D on muscle strength (Bischoff-Ferrari, Stahelin et al. 2000). In actual fact, high dose- vitamin D supplementation has been shown to significantly reduce the risk of falling in older individuals (Bischoff-Ferrari, Dawson-Hughes et al. 2009).

Calcium is the major component of the inorganic bone matrix. Achieving a good peak bone mass as a young adult contributes to a lesser impact of the physiological ageing process of the bone. Human requirements of calcium intake are higher in certain live stages, such as childhood, teen ageing, menopause and pregnancy; in elderly individuals calcium requirements also increase because of the decreased body capacity in absorbing the dietary calcium. Calcium supplements have been classically among general recommendations in osteoporosis management for decades, but more recently, scientific evidence has shown their minimal impact on BMD and fracture risk (Shea, Wells et al. 2004). Additionally, the observation that calcium supplements could be related with a higher rate of cardiovascular events and kidney stones have raised concerns about the risks and benefits of such intervention in osteoporotic patients (Bolland, Avenell et al. 2010; Reid 2014). With this, though, a more recent meta-analysis did not find any relationship between calcium supplements and rates of coronary heart disease-associated hospitalizations or deaths (Lewis, Radavelli-Bagatini et al. 2014). Still, guidelines recommend to educate individuals in an adequate calcium intake, from dietary source when possible. The IOF provides with a free-access calculator to estimate the personal

requirements and daily calcium intake based on regular diet (http://www.iofbonehealth.org/calcium-calculator).

1.5.4 Role of ethnicity and genetics in low bone mineral density and fracture risk

The variations in mean BMI have been advocated as one of the primary explanations behind the significant differences of mean BMD among different races (Nam, Shin et al. 2010; Yang, Lu et al. 2013). Other authors have found that some ethnicities reach their peak bone mass later than others and that could allow a better preservation of their BMD later in life (Berenson, Rahman et al. 2009; Yang, Lu et al. 2013). However, it's important to highlight that the extensive disparity of fracture rates among world regions cannot be explained only by such factors, and by contrast, fracture incidence among Asians, with relatively low average BMI and BMD, is generally lower than in Caucasian populations, despite the higher BMD in the latter (Sanchez-Riera, Wilson et al. 2010). In NHANES III, an important multi-ethnic population-based study in the United States, being non-Hispanic white was independently associated with a lower BMD and an increased risk for fracture (in comparison to be Mexican American or Black Americans), while the excess of risk due to FNBMD was comparable among the three ethnicities; that is, the fracture risk approximately doubled for each SD decrease in FNBMD regardless the ethnic group (Broussard and Magnus 2004; Looker, Melton et al. 2009).

Hip geometric parameters (longer hip axis length, increasing femoral neck/shaft angle and shaft cortical area) have been found to be independent predictors for hip

fracture among postmenopausal women (Faulkner, Cummings et al. 1993; Pulkkinen, Partanen et al. 2004; Gnudi, Sitta et al. 2007) and elderly men (Marshall, Zmuda et al. 2008), and have also been suggested to explain some of the important ethnic variations of fracture risk, (e.g. lower fracture risk among black and Asian men compared to white men) (Marshall, Zmuda et al. 2008).

Finally, there is also a significant hereditary component in the ability to retain bone mass and the risk to suffer a fracture. The genetic role has been demonstrated in twin studies (Slemenda, Christian et al. 1991; Arden and Spector 1997; Harris, Nguyen et al. 1998), as well as in the observation that family history of fragility fracture is a strong predictor of fracture risk; the RR of fracture is the highest when paternal/maternal history of hip fracture is present, which doubles the risk (Kanis, Johansson et al. 2004).

1.6 Diagnosis and Management of Osteoporosis

1.6.1 Diagnosis of osteoporosis and assessment of fracture risk

Osteoporosis is a skeletal disease where bone mass and bone architecture are compromised. Both elements play a key role in the bone strength and its susceptibility to fracture. Yet, from a practical point of view, diagnosis of osteoporosis is based in BMD, and WHO categories (i.e. normal, osteopenia and osteoporosis) are established upon the results of the BMD tested by DXA (Table 1.6).

Table 1.6. World Health Organisation's diagnostic thresholds for bone mineral density at spine, hip or distal forearm.

Diagnosis	BMD T-Score (SD units)
Normal	≥ -1
Low Bone Mass (Osteopenia)	< -1 but > -2.5
Osteoporosis	≤ -2.5
Severe Osteoporosis	≤ -2.5 plus one or more fragility fracture

However, it is important to differentiate such operational definitions from the assessment of the fracture risk and the intervention thresholds. In the clinical practice, doctors may decide to start pharmacological treatment in individuals with major risk factors for fracture, even in the absence of BMD measurement.

At present, there is no universally accepted policy for population screening to identify those individuals at high risk of fracture. Instead, patients are identified opportunistically using a case finding strategy when a previous fragility fracture or the presence of significant risk factors are present (Table 1.3). A general approach to risk assessment is shown in Figure 1.4 where subjects are screened for fracture probability based on their clinical risk factors. When probability of fracture is high, treatment is recommended independently of the results of the BMD test. In contrast, BMD information becomes more relevant in those cases where fracture probability is intermediate and BMD will lead to re-classify the case as having high or low risk of fracture. Finally, subjects falling into the low risk group, probably don't need neither screening with BMD testing nor pharmacological intervention. The assessment of

BMD is more commonly done with central DXA, but this basic decision making strategy is valid using other BMD testing methods, such as QUS or pDXA.

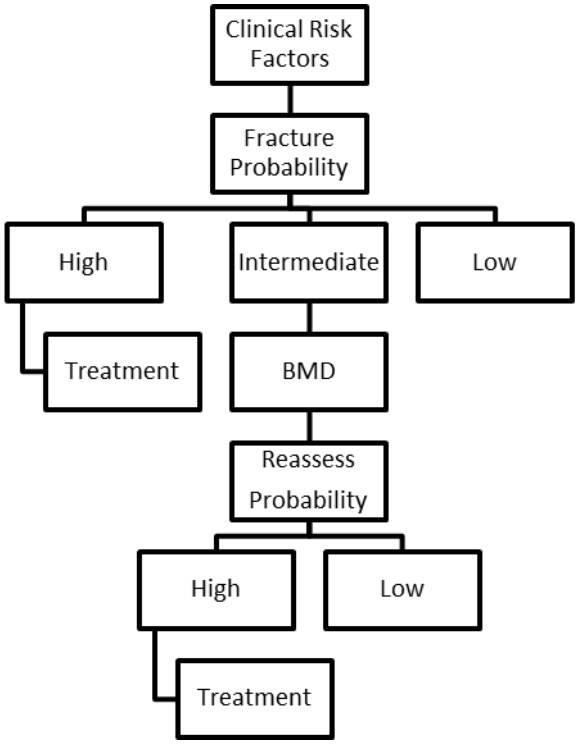

Figure 1.4. Fracture probability and decision making.

Adapted from Kanis JA et al 2009 (Kanis, Johansson et al. 2009)

Country-specific guidelines exist in regards to screening of individuals at high risk of osteoporosis, as well as management in primary and secondary prevention of fractures. Applicability of screening tools and interventional thresholds based on multifactorial risk assessments such as FRAX®, are variable depending on the geographical area. Reasons for this are multiple, such as the availability of DXA machines, the cost and availability of the main pharmacological interventions and the existence of cost-effectiveness studies in the target population (keeping in mind that fracture risk is country-specific). In countries with high access to densitometry,

referral for DXA is expected in any individual with any clinical risk factors for osteoporosis, and intervention is recommended when the algorithm of fracture probability integrating BMD indicates that the risk is above the interventional threshold (Figure 1.5).

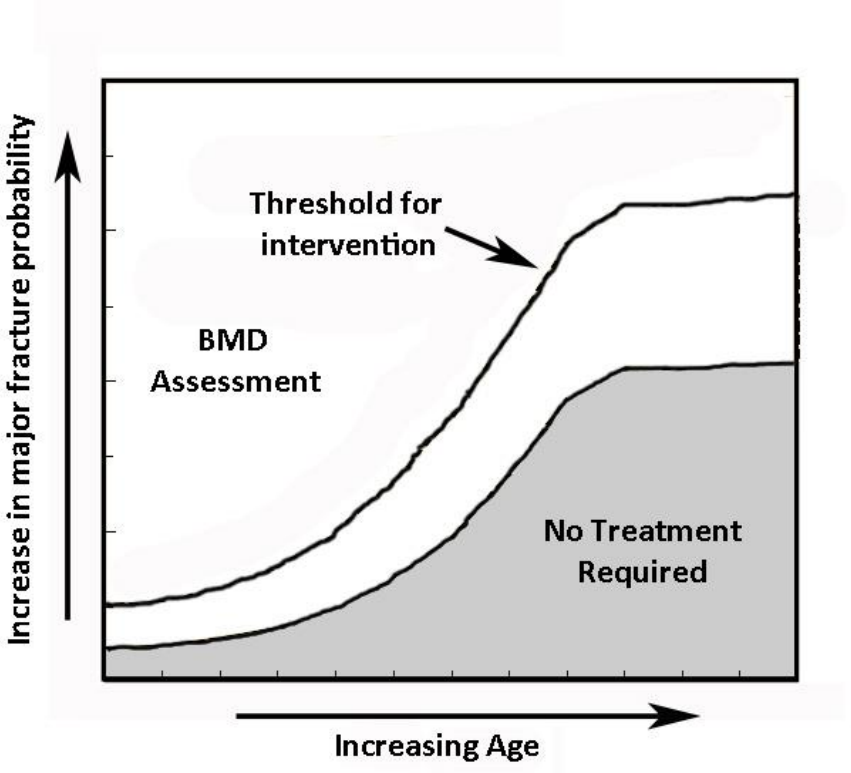

Figure 1.5 Assessment of fracture risk in countries with high access to Dual-X-Ray-Absorptiometry (DXA)

DXA is undertaken in women presenting with a clinical risk factor, while DXA assessment and/or treatment is not recommended where the FRAX® probability is lower than the lower assessment threshold (grey area). DXA measurement is recommended in the rest of the women and treatment recommended when the fracture probability exceeds the upper threshold intervention line. Adapted from Kanis JA et al 2013 (Kanis, McCloskey et al. 2013).

In contrast, countries with limited access to DXA, only individuals with an intermediate fracture probability are recommended to be sent for BMD testing (Figure 1.6) (Kanis, McCloskey et al. 2013).

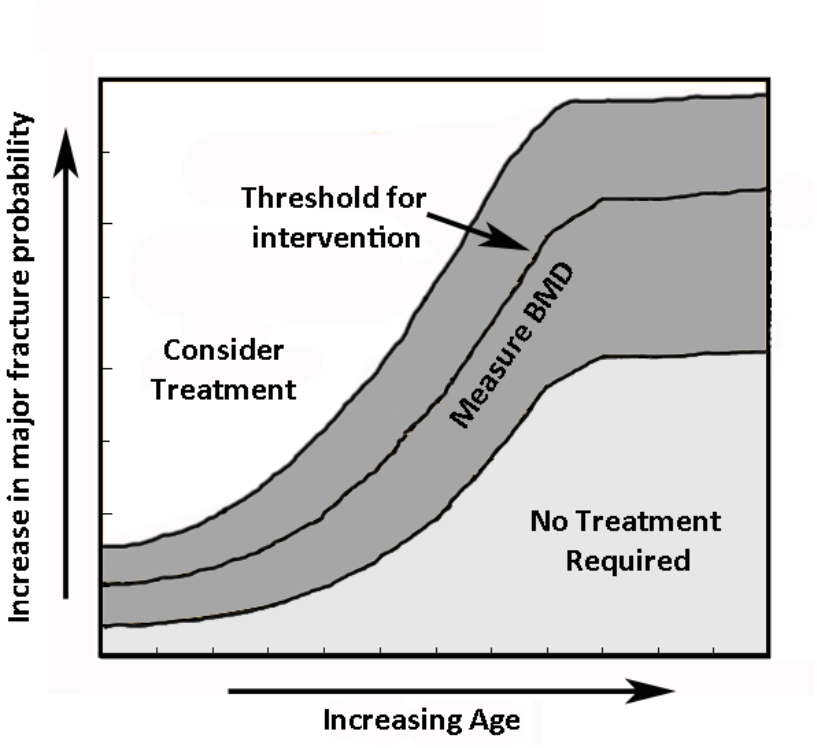

Figure 1.6. Assessment of fracture risk in countries with low access to Dual-X-Ray-Absorptiometry (DXA)

When fracture probability is first assessed without BMD information, DXA test is only recommended when the probability is intermediate (dark grey region). DXA assessment and/or treatment are not recommended where the FRAX® probability is lower than the lower assessment threshold (light grey area). Adapted from Kanis JA et al 2013 (Kanis, McCloskey et al. 2013).

Ultimately, assessment of fracture risk and the risk/benefit of intervention has to be individualized in each case taking into account other factors, such as comorbidities, insurance coverage, and compliance.

Apart from fracture risk evaluation, an initial diagnostic work-up is recommended in order to screen for secondary causes of osteoporosis (e.g: thyroid disease, hyperparathyroidism, malabsorption syndromes, etc) and allow differential diagnosis with other diseases that also present with low BMD and increased risk of fracture, such as osteomalacia and multiple myeloma (Table 1.7).

Table 1.7 Recommended procedures in the diagnostic work-up in patients with osteoporosis.

Routine
- Complete clinical history including screening of FRAX® clinical risk factors
- Physical Examination including height and weight
- Complete blood count, creatinine, serum calcium, alkaline phosphatase, serum phosphate, PTH, TSH, calcidiol (25-OH-VitD), albumin, liver transaminases, ESR
- Lateral radiograph of thoracic and lumbar spine
- Bone mineral density test (DXA) in hip and spine
- Lateral imaging DXA for vertebral fracture assessment (VFA)
In selected cases
- Markers of bone turnover
- Serum or urine protein electrophoresis, fasting and 24-h urinary calcium, urinary free cortisol, IgA anti-tissue transglutaminase antibody or IgA

endomysial antibody

- FSH, LH, prolactin, free testosterone
- Trans-iliac bone biopsy
- DXA in distal radius
- Other BMD measurement methods (QUS, pDXA, QCT)

Markers of bone turnover when available and mainly for research purposes. DXA in distal radius if DXA in central sites (hip and spine) is not applicable (e.g. hip replacements). Other BMD measurement methods when DXA is not available. FRAX®: fracture risk assessment tool; PTH: parathyroid hormone; TSH: thyroid stimulating hormone; ESR: erythrocyte sedimentation rate; DXA: dual-X-ray-absorptiometry; QUS: quantitative ultrasound; pDXA: peripheral DXA; QCT: quantitative computerized tomography.

1.6.2 General management: non-pharmacological interventions

1.6.2.1 Physical activity and prevention of falls

Immobilization constitutes an important cause of bone loss, and should always be avoided when possible (e.g. prolonged hospitalisations, elderly living in age care facilities, etc). In contrast, physical activity has a positive impact in bone mass, muscle strength and balance, as exposed in the previous chapter. Risk factors for falls (Table 1.8) should be identified and corrected or minimised if feasible (e.g. by prescribing walkers in those with impaired gait, correcting visual loss, reducing medication that alters balance, etc), together with improvement of the home environment (shower chairs, handrails, ground obstacles, etc).

Table 1.8 Common risk factors associated with falling

Risk Factors Associated with Falls
Age
Cognitive Impairment
Heart disorders
History of falls
Impaired gait and balance
Impaired mobility and disability
Impaired vision
Medication
Neurological disorders
Neuromuscular or musculoskeletal disorders

Adapted from Kanis et al (Kanis, McCloskey et al. 2013)

Hip protectors have been used in several randomized controlled trials in order to reduce hip fracture after falls. While it seems that they might collaborate in reducing hip fracture incidence in nursing care facilities, data suggests that they may mildly increase the rate in pelvic fractures (Santesso, Carrasco-Labra et al. 2014). Additionally, they show low acceptance and adherence among the older population, and therefore, the use of hip protectors still remains controversial.

1.6.2.2 Nutrition

Adequate intake of calcium, vitamin D and proteins are required to achieve a good musculoskeletal health during all human life. In older individuals is important to maintain a good level of such nutrients to avoid sarcopenia and osteoporosis. The capacity of the skin to synthesize vitamin D from the sunlight exposure diminishes with age, and hours of outdoor life tend to decrease in the older population. Therefore, most of the individuals diagnosed with osteoporosis require supplements of vitamin D. Additionally, there is a high prevalence of insufficient calcium and protein intake in the elderly.

The ESCEO recommends optimal dietary protein intake of 1.0-1.2g/kg of bodyweight per day with at least 20-25g of high-quality protein at each main meal, with adequate vitamin D intake at 800IU/d to maintain serum 25-hydroxyvitamin D levels >50nmol/L as well as calcium intake of 1000mg/d, alongside regular physical activity/exercise 3-5 times/week combined with protein intake in close proximity to exercise, in postmenopausal women for prevention of age-related deterioration of musculoskeletal health (Rizzoli, Stevenson et al. 2014). Dietary sources of calcium are the preferred option, and calcium supplementation should only be targeted to those who do not get sufficient calcium from their diet and who are at high risk for osteoporosis or they have already been diagnosed.

1.6.3 Major pharmacological interventions

Several agents are approved for the treatment of osteoporosis. They have all shown to increase BMD and reduce the risk of vertebral fracture in randomized clinical trials. Some have also shown to reduce the risk of non-vertebral fractures, and in some cases, the risk of hip fracture (Table 1.9). Risk reductions of between 30-70 % have been demonstrated for vertebral fractures, around 15-20 % for non-vertebral fractures and up to 40% for hip fracture (Kanis, McCloskey et al. 2013). Mortality reduction has been estimated in around 11% globally in one meta-analysis including four different agents (risedronate, zoledronic acid, strontium ranelate and denosumab) (Bolland, Grey et al. 2010).

Table 1.9 Anti-fracture efficacy of the most commonly used treatments for postmenopausal osteoporosis

	Effect on non-vertebral fracture risk		Effect on vertebral fracture risk	
Treatment	**Osteoporosis**	**Established Osteoporosis [a]**	**Osteoporosis**	**Established Osteoporosis [a]**
Alendronate	+	+	NA	+ (including hip)
Denosumab	+ [b]	+	+ (including hip)	+ [b]
HRT	+	+	+	+ (including hip)
Ibandronate	NA	+	NA	+ [c]
Raloxifene	+	+	NA	+
Risendronate	+	+	NA	+ (including hip)
Strontium ranelate	+	+	+ (including hip [c])	+ (including hip [c])
Teriparatide and PTH	NA	+	NA	+ [d]
Zolendronic Acid	+	+	NA	+ [b]

Fracture efficacy when taken with calcium and vitamin D supplements. Results of randomized controlled trials. NA: no evidence available; +: effective drug; a: women with a prior vertebral fracture; b: mixed group of patients with or without prevalent vertebral fractures; c: in subsets of patients only (post hoc analyses): d: shown for teriparatide only. Adapted from Kanis JA et al 2013 (Kanis, McCloskey et al. 2013).

The mechanism of action of such drugs is diverse, but most of the agents produce their effect through the inhibition of bone resorption, except recombinant parathyroid hormone (1-34 PTH and 1-84 PTH), which given at small doses intermittently, stimulate osteoblastic line and lead to bone formation. Strontium ranelate, despite being mainly an inhibitor of bone resorption, has also shown some simultaneous stimulation on osteoblast activity.

Benefits from concomitant use of such agents have not been fully demonstrated yet. Instead, sequential treatment, particularly the administration of an inhibitor of bone resorption following PTH analogs, may potentiate the benefits obtained during the anabolic treatment (Black, Bilezikian et al. 2005; Eastell, Nickelsen et al. 2009).

In general, safety profile of all major pharmacological intervention is quite favorable (Kanis, McCloskey et al. 2013). One exception is the use of hormonal replacement therapy (HRT), which is not recommended as first line for the treatment of osteoporosis anymore given the increased risk in cardiovascular events and breast cancer (Kanis, McCloskey et al. 2013). Most of guidelines only recommend HRT for climacteric symptoms and with a total accumulative dose as small as possible. Other treatments, such as calcitonin and vitamin D derivates (i.e. alfacalcidiol), have been abandoned due to their low cost-effectivity and the presence of risks (e.g. cancer in long-term use of calcitonin; hypercalcemia and nephrocalcinosis in alfacalcidiol) that possibly outweigh the potential benefits. More recently, the European Medicines Agency (EMA) has put a black box warning for strontium ranelate in patients with known cardiovascular disease.

Screening strategies followed by pharmacological interventions have shown to be cost-effective in osteoporosis (Schousboe, Ensrud et al. 2005; Mobley, Hoerger et al. 2006; Hiligsmann, Gathon et al. 2010; Nayak, Roberts et al. 2011). In addition, cost-effectivity in the prevention and treatment of osteoporotic fractures has been established for all major pharmacological interventions individually (Strom, Borgstrom et al. 2007; Borgstrom, Strom et al. 2010; Hiligsmann, Vanoverberghe et al. 2010; Jonsson, Strom et al. 2011; Pham, Datta et al. 2011; Nayak, Roberts et al. 2012; Hiligsmann, Ben Sedrine et al. 2013; Hiligsmann, Boonen et al. 2013; Majumdar, Lier et al. 2013; Kim, Svedbom et al. 2014; Parthan, Kruse et al. 2014). Taking into account the lack of head-to-head randomized controlled trials and the absence proof of one treatment being clearly superior to another in terms of efficacy, first line and second line interventions are often based on the product's price. For this reason, generic alendronate tends to become first line option in lots of public health systems, while PTH analogues are reserved only for severe cases non responding adequately to antiresorptive therapy (Strom, Borgstrom et al. 2013). However, aspects related to tolerability and adherence to medications can highly impact the cost-effectivity of osteoporosis screening and treatment (Hiligsmann, Gathon et al. 2010), and they need to be considered both in population economic analysis as well as in individual decisions during clinical practice.

1.6.4 Invasive interventions: vertebroplasty and kyphoplasty

In patients with acute vertebral fracture with persisting pain despite optimization of analgesia, injection of cement in the fractured vertebral body without (vertebroplasty) or with preceding balloon inflation (kyphoplasty) may lead to short-term reduction of

pain. Their use is been controversial, particularly after a randomized controlled trial showing no beneficial effect versus placebo (Buchbinder, Osborne et al. 2009; Kroon, Staples et al. 2014). Furthermore, concerns exist about a possible increased risk of subsequent vertebral fracture after vertebroplasty, even though this conception has not been confirmed (Han, Wan et al. 2014; Kroon, Staples et al. 2014).

These techniques are exclusively for pain management and cannot substitute the rest of interventions for secondary prevention of fractures.

1.6.5 Monitoring of treatment

Compliance with anti-osteoporosis medications affects significantly their anti-fracture efficacy (Curtis, Westfall et al. 2008; Patrick, Brookhart et al. 2010). Poor adherence to medical therapies is a widespread public health problem. In osteoporosis, maybe because of being a silent disease for a big proportion of treated individuals with no history of fractures, compliance and persistence with treatment are poor. It is been estimated that approximately 50% of patients do not follow their prescribed treatment regimen or discontinue treatment within one year (Compston and Seeman 2006) Thus, it is important to check tolerability and adherence to pharmacological interventions in subsequent visits after starting bone therapies.

The goal of bone therapies is to improve bone strength and subsequently reduce the risk of fracture. It is likely that the long-term anti-fracture efficacy of anti-osteoporosis medications is only partly dependent on the extent to which they increase or

maintain BMD (Rabenda, Bruyere et al. 2011). Anyhow, BMD is one of the major predictors of bone strength, and it constitutes an objective, non-invasive and reproducible measurement to monitor treatment-related changes in the bone. In addition, evidence supports the correlation between the change in BMD and fracture risk reduction (Hochberg, Greenspan et al. 2002; Delmas, Li et al. 2004). Serial BMD testing can detect non-responding individuals by finding loss of bone density, suggesting the need for re-evaluation of diagnosis and treatment. As per recommendations of the ISCD, follow-up BMD testing should be done when the expected change in BMD equals or exceeds the least significant change (LSC), to ensure that the BMD change detected is real. The LSC is related to the measurement variability of the technique itself. Typically one year after initiation or change of therapy is appropriate, with longer intervals once therapeutic effect is established (The International Society for Clinical Densitometry. 2007).

Several bone markers from serum and urine can be used to monitor the rate of bone formation and bone resorption. The most broadly used are procollagen I N-terminal extension peptide (P1NP) for bone formation and C-telopeptide breakdown products (especially serum Carboxy-terminal collagen crosslinks or CTX) for bone resorption. Changes in bone markers once treatment is started occur typically before detectable BMD changes (within the first 3-6 months). Early change in bone markers have been correlated with future increases in BMD, and importantly, to vertebral fracture risk reduction in antiresorptive therapies. (Reginster, Collette et al. 2008). However, the effect on bone markers does not seem to be determinant in the choice of an anti-osteoporosis therapy, and more research is still required to establish standardized use of those in the clinical practice.

Duration of treatment will first depend on individual medical reasons. In general, evidence of fracture risk reduction is been shown up to 5 years for some of the antiresorptive drugs, and up to 10 years for strontium ranelate. On the other hand, use of PTH analogues is only approved for a 24-month period. In general, long-term safety is good for most of the drugs (Cooper, Reginster et al. 2012). Exceptions to this, as mentioned previously, are the long-term use of HRT and calcitonin, as well as the prolonged use of bisphosphonates, the latter due to occurrence of subtrochanteric femoral fractures, despite this being a rare secondary effect (Black, Kelly et al. 2010; Rizzoli, Akesson et al. 2011). Sequential treatment is advisable in those patients exhibiting high risk of fracture despite long-term antiresorptive therapy, who might benefit from anabolic treatment, followed by resuming antiresorptive therapy upon finalization of PTH analogues (Black, Bilezikian et al. 2005; Eastell, Nickelsen et al. 2009; Boonen, Milisen et al. 2011). Even though optimized improvement of BMD is been achieved on combination treatment (simultaneous administration of antiresorptive and anabolic therapy) (Muschitz, Kocijan et al. 2013; Walker, Cusano et al. 2013; Leder, Tsai et al. 2014), the influence of such approach on fracture risk and the cost-effectivity of this type of intervention is not well established yet, and therefore, not globally recommended in the clinical practice.

1.7 Osteoporosis in the real world: underdiagnosed and undertreated

It has been exposed in a previous chapter how enormous the costs from fragility fractures are, and the way the ageing of the global population will affect the increasing economical toll that societies will face soon.

Recent reviews have demonstrated the cost-effectiveness of treating osteoporosis (Zethraeus, Borgstrom et al. 2007; Strom, Borgstrom et al. 2013). Branded alendronate showed to be cost-effective in nine countries of Western Europe in a longitudinal fracture intervention trial (Strom, Borgstrom et al. 2007), and complementary data indicates that the cost-effectivity of such intervention is probably maintained in both men and women over 50 years of age at high risk of fracture in most Western countries (Strom, Borgstrom et al. 2013). Cost-effectiveness improves with the number of risk factors (Strom, Borgstrom et al. 2013). Furthermore, other authors have shown that the cost-effectiveness of screening and treatment of osteoporosis with alendronate is cost-effective for all alendronate price ranges in the United States, and even cost-saving for the cheapest formulations (Nayak, Roberts et al. 2012).

It is also been highlighted before that, the ability of hypertension and hypercholesterolemia to predict stroke and myocardial infarction, respectively, are not better than the predictive value of BMD to predict fractures (Marshall, Johnell et al. 1996). In addition, cost-effectiveness of therapeutical intervention for the three risk factors has shown to be cost-effective for each of them at a population level

(Zethraeus, Strom et al. 2008). What's more, the cost-effectivity improves with age for osteoporosis treatment, but not always for cholesterol lowering and antihypertensive therapy (Zethraeus, Strom et al. 2008).

These observations contrast enormously with the lack of osteoporosis screening and treatment among people suffering fragility fractures (Strom, Borgstrom et al. 2013). Systematic review of international studies have shown that most of the patients are not offered proper osteoporosis management after the acute care of a fragility fracture, including low rate of laboratory tests and BMD testing referrals (less than one third of the patients), as well as low rate of pharmacological interventions in those with osteoporosis diagnosis, with less than 20% of patients discharged in any bone medication (Elliot-Gibson, Bogoch et al. 2004; Giangregorio, Papaioannou et al. 2006). In contrast, more than 75% of elderly patients discharged after a myocardial infarction are prescribed beta-blockers as secondary prevention of ischemic heart disease (Austin, Tu et al. 2008), which clearly shows the gap of disease awareness among osteoporosis and cardiovascular diseases.

Despite some efforts towards the implementation of systematic screening of osteoporosis in population at high risk of fracture, there is still a generalized lack of awareness of the magnitude of the problem both by professionals and patients. Still, osteoporosis doesn't count among top research and public health priorities (Daar, Singer et al. 2007). A paradigm of this, it's the no appearance of any musculoskeletal condition among the health priorities of WHO for non-communicable diseases, with no mention either of BMD or fractures (www.who.int).

1.8 Context of the Thesis Project: The Global Burden of Diseases 2010 Study (The GBD 2010 study)

The Global Burden of Diseases (GBD) taskforce started in 1990 as a World Bank initiative to estimate the health burden of the main diseases and injuries in the world in a comparable, systematic, and rigorous epidemiological manner (Murray, Lopez et al. 1994). The initiative involved the collaboration among epidemiologists and public health experts from different universities and institutions throughout the world. The health burden resulting from 109 health conditions was assessed through data review on the incidence, prevalence and mortality from all countries. The first GBD Study 1990 generated widely published findings and comparable information on the burden of disease for all the world. From 2000 to 2004, albeit only for some diseases, the WHO updated these data (Lopez, Mathers et al. 2006), and multiple regional- and country-specific reports as well as disease-focused burden analysis, have been generated since then. These burden estimates have been used by governments and non-governmental agencies to establish priorities for research, health policies and funding. The Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) was implemented from 2007 to 2012 as a collaboration of seven institutions: the Institute for Health Metrics and Evaluation (IHME) as the coordinating center providing academic leadership; the University of Queensland School of Population Health; the WHO; the Johns Hopkins Bloomberg School of Public Health; the Harvard School of Public Health; Imperial College London; and the University of Tokyo (Murray, Lopez et al. 2007) (Figure 1.7. The Global Burden of Diseases 2010 study timeframe.). The GBD 2010 study was undertaken to update and revise previous GBD studies, addressing key limitations of

previous studies by using updated and more advanced methods. The improvements in the methodology included a more standardized approach to evidence synthesis, inclusion of assessments of comorbidity and uncertainty around estimates, and more specific breakdowns of the data. For example, the GBD 1990 used a modification of World Bank regions to divide the world into 8 groups. These were modified in the GBD 2000 to start with the six political regions of WHO and then subdivided into 14 regions based on estimates of adult and child mortality available at that time. For the GBD 2010, 21 world regions were created on the basis of two criteria: epidemiological homogeneity and geographic contiguity. For some types of analysis in the GBD, seven super-regions, which cluster together related groups of regions on the basis of cause of death, were created. Age groups were amplified from 8 (in the GBD 2000) to 20 groups in the GBD 2010 study. The list of health causes also expanded, from 134 of the original GBD 1990 to 291 diseases and injuries of the GBD 2010, and so did the risk factors, from 27 in the GBD 2000 to 67 in the GBD 2010 (Lim, Vos et al. 2012; Murray, Vos et al. 2012; Vos, Flaxman et al. 2012).

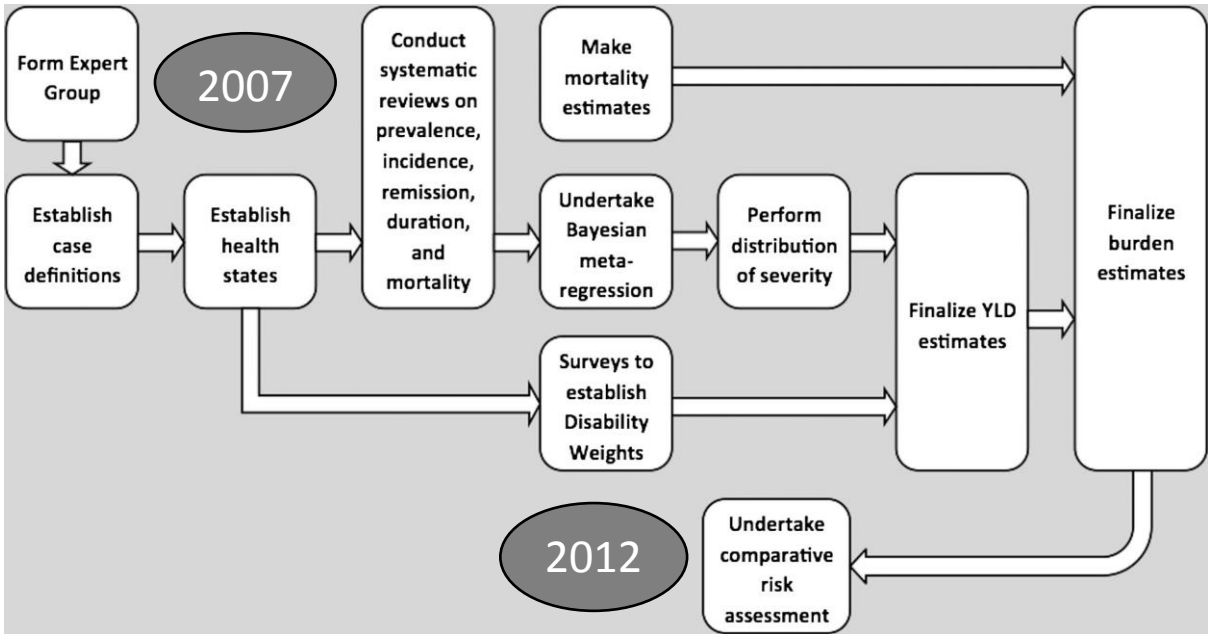

Figure 1.7. The Global Burden of Diseases 2010 study timeframe.

Steps taken from formation of expert groups in 2007 to publication of main estimates end 2012 in Lancet. Adapted from Hoy D et al 2014 (Hoy, Smith et al. 2014).

Prevalence data were gathered through systematic reviews, with variability between studies regarding case definition, age groupings and prevalence period used. In addition, data were often missing for specific age groups, regions and years of interest. A Bayesian meta-regression tool, DisMod-MR (DISease MODelling Meta-Regression), was developed by the Core Team (CT) specifically for the GBD 2010 study to deal with these challenges (Vos, Flaxman et al. 2012). In brief, DisMod-MR is a tool that helps to pool heterogeneous data presented in different age groups; to adjust data for methodological differences; to check data on incidence, prevalence, duration, remission and mortality risk for internal consistency; and to predict values for countries and regions with little or no data using disease-relevant country characteristics (such as average BMI in knee osteoarthritis) and random effects for country, region and super-region.

The two primary outcome measures for the GBD work include Deaths and DALYs, which combine the years lived with disability (YLDs) and the years of life lost due to premature mortality (YLLs). One DALY can be thought as the loss of one year of 'healthy' life. DALYs used in burden measurement are the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability. This measure allows comparisons of the burden caused by different conditions on the overall health status, as well as comparisons between countries, regions, age groups and genders.

The number of 'incident YLDs' are calculated by the number of incident cases x the average duration (expressed in years) x the Disability Weight (DW). Prevalent YLD is the other form of YLD's and can be calculated as prevalence x DW. The DW goes from zero (a health state equivalent to ideal health) to one (a health state equivalent to death).

Then,

DALY= YLL + YLD

where:

YLL=*years of life lost due to premature mortality*; **YLD**=*years lived with disability*

and

YLL = N x L

where N = *number of deaths*; **L** = *standard life expectancy at age of death in years*

YLD = I x DW x L

where **I** = *number of incident cases*; **DW** = *disability weight*; **L** = *average duration of the case until remission or death in years*

The initiative attributes DWs to different health states in order to calculate DALYs. In GBD methodology, the term “sequela" includes severity and disabling consequences of a disease. Partitioning a condition into a series of sequelae enables disability variations within a condition to be taken into account through the application of different DWs to the different sequelae (recognizing, for example, the diverse disabling consequences of mild OA and severe OA). Disease definitions, range of disease severity and functional health sequelae resulted from literature review or, in absence of published evidence, through expert group consensus with initial concept mapping followed by a series of modified Delphi exercises. The aim was to describe the “average” or “typical” common general manifestations within each condition. Health states were mapped to standardised health check-lists to describe functional impairment (Salomon 2008; Salomon, Vos et al. 2012). In that way, for the latest revision of the GBD (GBD 2010), YLDs have been computed for 1160 sequelae resulting from 289 disease and injury causes, by multiplying the number of people living with each sequela by an associated disability weight (Figure 1.8). The 1160 sequelae were mapped into a set of 220 distinct health states that capture the most salient differences in symptoms and functioning.

To produce DWs, surveys were conducted through personal interviews in Bangladesh, Indonesia, Peru, and Tanzania; telephone interviews in the United States; and an open-access web-based survey. In household surveys, households were randomly selected with a multistage, stratified sampling design, with probabilities of being selected proportional to population size. All samples were designed to be representative in a specific geographical area or, in the case of the USA, to be nationally representative. The surveys used paired-comparison

questions, in which respondents considered two hypothetical individuals with different functional limitations (corresponding to a randomly selected pair of health states), and indicated which person they regarded as healthier. The web survey added ‘population health equivalence’ questions, which compared the overall health benefits of different life saving or disease prevention programs. Paired comparison responses were analysed using probit regression analysis, and results were anchored on a scale from 0 (implying no loss of health) to 1 (implying a health loss equivalent to death) using results from the population equivalence responses to estimate disability weights for all 220 unique health states in the study.

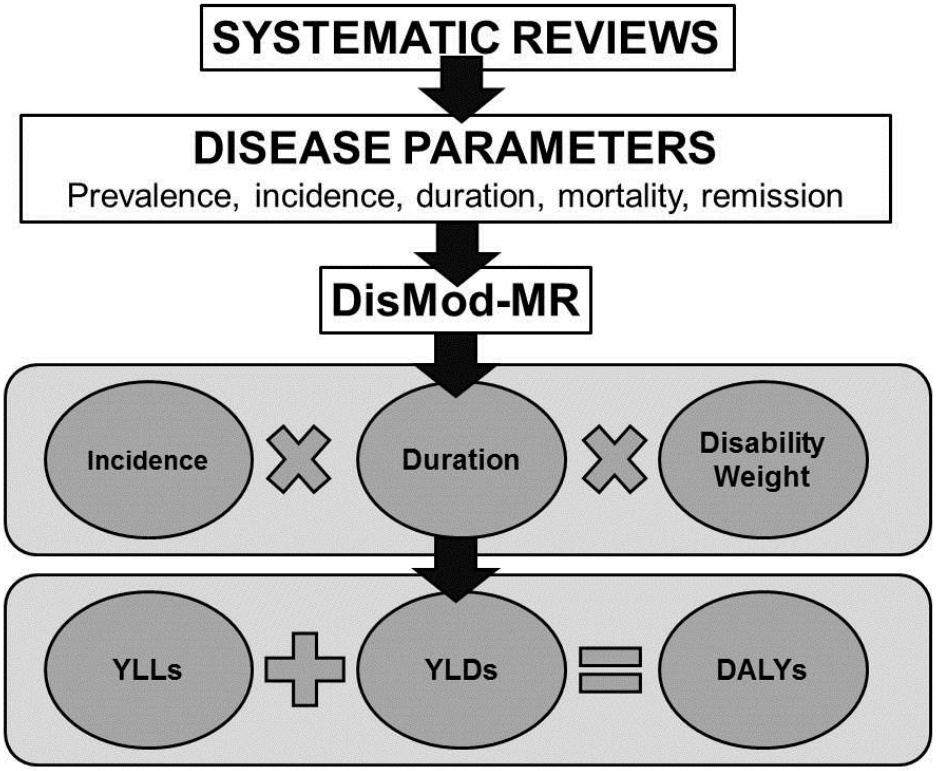

Figure 1.8 Steps for the production of health burden

The Dismod-MR program adjusts for heterogeneity, derives missing values, ensure internal consistency, and produces estimates cause-sex-age-region-specific. DisMod-MR: Disease modelling meta-regression tool; YLLs: years of life lost due to premature mortality; YLDs: years lived with disability; DALY: disability-adjusted life years.

Out the 291 causes of health burden in the GBD 2010 study, 235 were causes of mortality (Lozano, Naghavi et al. 2012). For the YLLs calculations, database development was based in vital registration with medical certification of deaths, verbal autopsy data, police and crime reports, maternal mortality surveillance, population-based cancer registries, burial and mortuary data, and hospital-based deaths. The last three sources of data were only chosen for deaths due to injuries.

The model used a common framework for all causes of mortality to allow all cause-specific deaths to equal the total number of deaths from all causes in each country, region, gender and age group (Lozano, Naghavi et al. 2012).

One of the main limitations of the GBD initiative is that burden estimates are limited to the impact of the different causes on individual health. It does not count for the burden that conditions may cause into family structures, workforce and economic burden for the societies. Despite the GBD study represents the most important effort to summarize the health burden of the main causes in a comprehensive and comparative manner, social and economic outcomes of health conditions are equally relevant to properly plan public health strategies. This is particularly important at a regional level, because of the different access and cost to screening tools and treatments across the different countries in the world.

The core papers with the main results from the GBD 2010 study were published in *Lancet* in December 2012 (Lim, Vos et al. 2012; Lozano, Naghavi et al. 2012; Murray, Vos et al. 2012; Salomon, Vos et al. 2012; Vos, Flaxman et al. 2012). Since then, disease-focused and regional reports have been published in order to disseminate results more widely. Detailed data on methods and burden estimates can be found open access in the IHME website (http://www.healthdata.org/gbd).

This project is part of the Musculoskeletal (MSK) Expert Group (EG) series within the GBD 2010 study, based in the Institute of Bone and Joint Research in the University of Sydney and led by Professor Lyn March. The MSK EG was part of cluster C led by one of the CT members in the University of Queensland (Figure 1.9), Theo Vos.

Extended reports on the overall methods for MSK conditions (Hoy, Smith et al. 2014), global burden of osteoarthritis(Cross, Smith et al. 2014), rheumatoid arthritis (Cross, Smith et al. 2014), gout (Smith, Hoy et al. 2014), low back pain (Hoy, March et al. 2014), neck pain (Hoy, March et al. 2014), occupationally-related low back pain (Driscoll, Jacklyn et al. 2014), other musculoskeletal conditions (Smith, Hoy et al. 2014), and final conclusions (Hoy, Smith et al. 2014) were published in the first half of 2014 in *Annals of Rheumatic Diseases*.

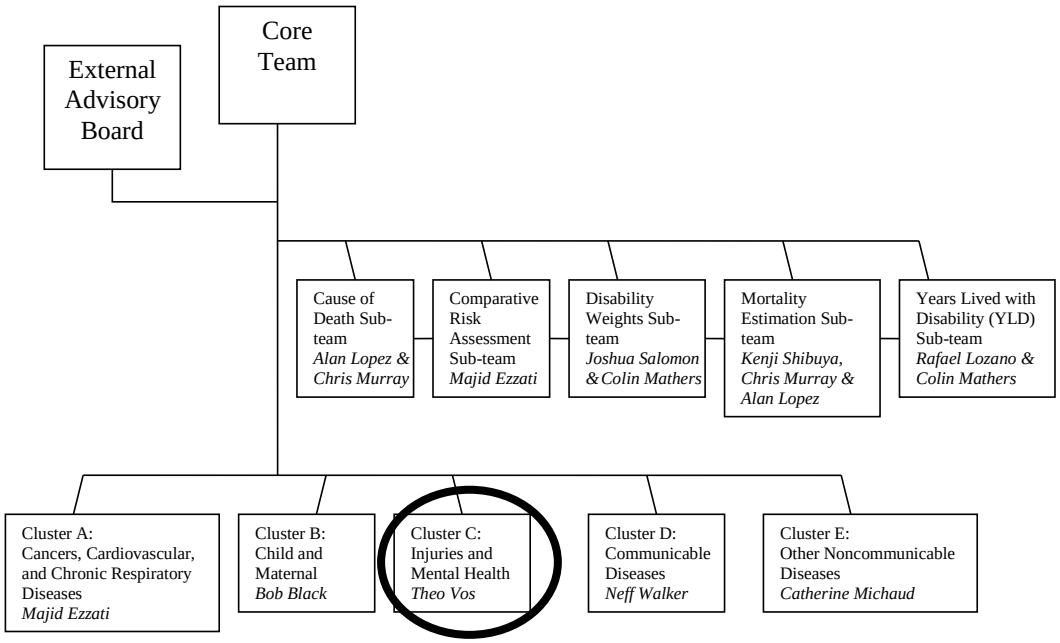

Figure 1.9 The Musculoskeletal Expert Group as part of cluster C that included also the Injuries and Mental Health Expert Groups.

Cluster C was led by one of the core team members in University of Queensland. Modified from the GBD Operations Manual.

Details on the results from the GBD 2010 study are out of the scope of this present work and all data can be found free of charge in the Lancet core papers (Lim, Vos et al. 2012; Lozano, Naghavi et al. 2012; Murray, Vos et al. 2012; Salomon, Vos et al.

2012; Vos, Flaxman et al. 2012) and in the IHME website (http://www.healthdata.org/gbd). Briefly, DALYs remained stable from 1990 (2.503 billion) to 2010 (2.490 billion). However, the crude rate of DALYs per 1000 people decreased in 23% during the same time period, showing the improvement trend in the global health burden over the last two decades. The changes in the global health were marked by two important facts, which were the increase of life expectancy and the global shift from communicable to non-communicable causes. The first was highly influenced by the reduction of mortality due to maternal, newborn and nutritional causes, and communicable diseases in general. As per non-communicable causes, such as ischemic heart disease and diabetes, they increased around 30% from 1990 to 2010, contributing enormously to the worldwide increase in YLD. Of the global DALYs for 2010, loss of life due to premature mortality (YLLs) and loss of life due to disability (YLDs) represented 68.8% and 31.2%, respectively, of the total DALYs. Cardiovascular diseases were the leading causes of YLLs worldwide, while mental and behavioural disorders ranked first among causes of YLDs, followed by musculoskeletal disorders, representing 22.7% and 21.3%, respectively, of all YLDs worldwide. Low back pain ranked first in the top causes of YLD's both in 1990 and 2010. Neck pain and other MSK disorders (including diseases such as systemic lupus erythematosus) ranked within the top 10 causes of disability both for 1990 and 2010, and osteoarthritis significantly increased its rank from 15th to 11th between 1990 and 2010. Falls also ranked relatively high in disability burden (number 10 in the rank list of YLD causes for 2010), with only a small ranking shift over the 20-year period (Figure 1.10).

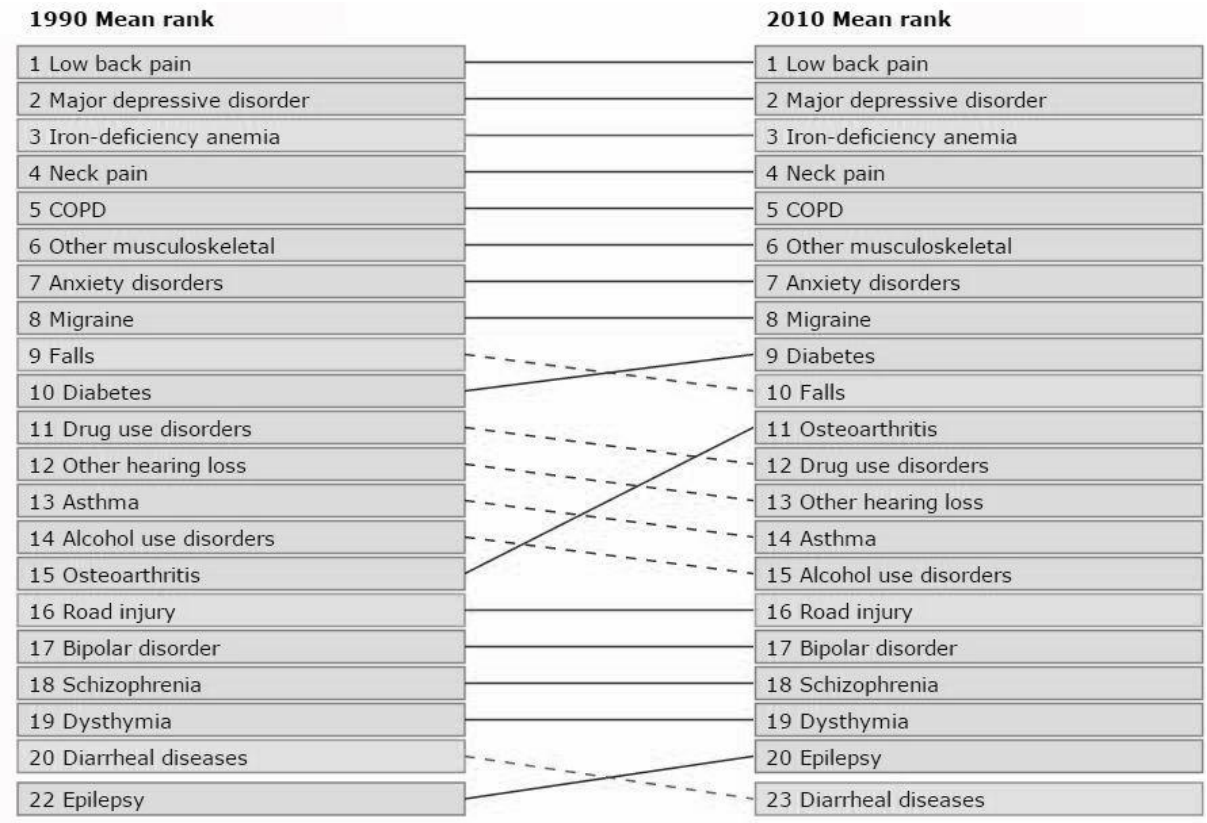

Figure 1.10. Top Twenty Causes of Years Lost Due to Disability (YLDs)

Continuos lines indicate no change or increase of rank from 1990 to 2010, while dotted lines denotes a decrease in the rank. Adapted from IHME website (http://www.healthdata.org/gbd).

In previous editions of the GBD initiative, the health burden of osteoporosis was reflected through the burden of osteoporotic fractures. For the year 2000, 9.0 million osteoporotic fractures were estimated to occur worldwide, of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures. The greatest number of fractures occurred in Europe (34.8%). Almost 6 million DALYs were lost in the world due to osteoporotic fractures, half in Europe and in the Americas. In Europe, osteoporotic fractures accounted for more DALYs lost than all causes of cancer except lung cancer, and among MSK causes, DALYs lost in

Europe due to osteoporosis (2.0 million) were less than for osteoarthritis (3.1 million) but greater than for rheumatoid arthritis (1.0 million) (Johnell and Kanis 2006).

Osteoporosis per se was not considered as a disease in the GBD 2010 study, and for the first time, low BMD was included in the global burden estimates, as a risk factor for fractures, which represented a proportion of the global burden from falls (Figure 1.11). The present project describes the methods used to calculate the contribution of low BMD to the global health burden due to falls and presents results on the estimates of the burden of low BMD by age, sex, and world region, both for 1990 and 2010. Comparative risk assessment (CRA) methodology was used to calculate the burden estimates, following the risk factor analysis within the GBD 2010 study (Lim, Vos et al. 2012).

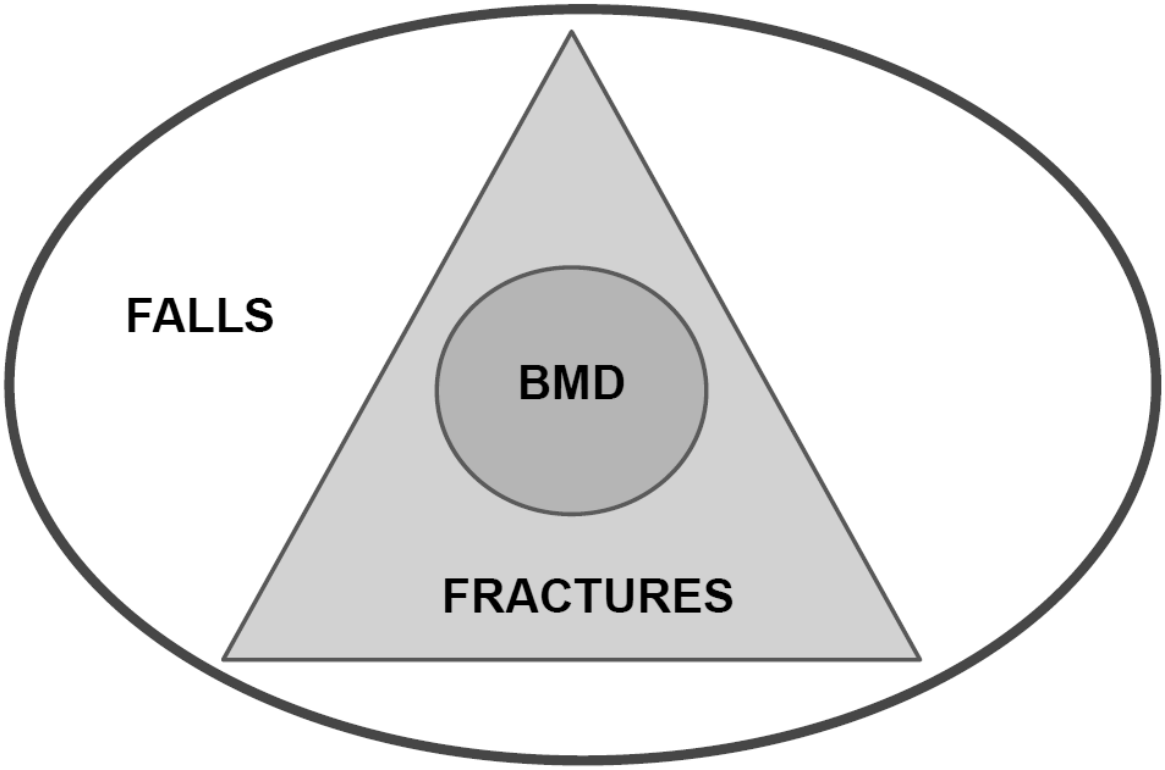

Figure 1.11. Burden Due to Low Bone Mineral Density in the GBD 2010 Study.

The burden attributable to low BMD is calculated as part of the burden due to fractures, which is part of the burden associated with falls in the GBD 2010 study. BMD: bone mineral density.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypotheses:

1) An important percentage of the global health burden due to falls could be potentially avoided in the hypothetical scenario that the aged global population presented an ideal bone mineral density (BMD).
2) The global burden due to low BMD is expected to have increased in the last 20 years with the growth of ageing populations in all world regions. The burden can vary depending on the world region, the age group and the sex.

2.2 Objectives:

1) To estimate the global levels of BMD measured by dual-x-ray-absorptiometry at femoral neck in populations 50 years and over as the exposure variable for 1990 and 2010.
2) To estimate the global burden of low bone mineral density as a fraction of the global burden due to falls for 1990 and for 2010.
3) To estimate the percentage of the global health burden attributable to low BMD for 1990 and 2010.
4) To estimate the global number of deaths due to low BMD for 1990 and 2010.
5) To estimate the global number of Disability-adjusted life years (DALYs) due to low BMD for 1990 and for 2010.
6) To compare the health burden of low BMD to that derived from other risk factors within the Global Burden of Diseases 2010 Study.

3 METHODOLOGY

3.1 Introduction to Comparative Risk Assessment Methodology

In Comparative Risk Assessment (CRA) methodology (Ezzati, Hoorn et al. 2011; Lim, Vos et al. 2012), the health burden due to a risk factor is compared to the hypothetical burden that would occur if the risk factor distribution was at the optimal level. Estimates are based on a *counterfactual* exposure distribution that would result in the lowest population risk exposure, referred to as the *theoretical-minimum-risk exposure distribution* (TMRED) (Figure 3.1). This has to be theoretically possible based on current scientific evidence, irrespective of whether currently attainable in practice. As a result, the CRA methodology maps alternative population health scenarios that arise from changes in the distribution of exposure to risk factors.

Using the exposure distributions to the risk factor and the risk relationship between the risk factor and a health outcome, *population attributable fractions* (PAFs) are then calculated using the following formula:

$$PAF = \frac{\int_{x=0}^{m} RR\,(x)P(x)dx \; - \; \int_{x=0}^{m} RR\,(x)P'(x)dx}{\int_{x=0}^{m} RR\,(x)p(x)dx}$$

where *PAF* is the population attributable fraction, *RR(x)* is the relative risk at the exposure level *x*, *P(x)* is the population distribution of exposure, *P'(x)* is the counterfactual distribution of exposure, and *m* the maximum exposure level.

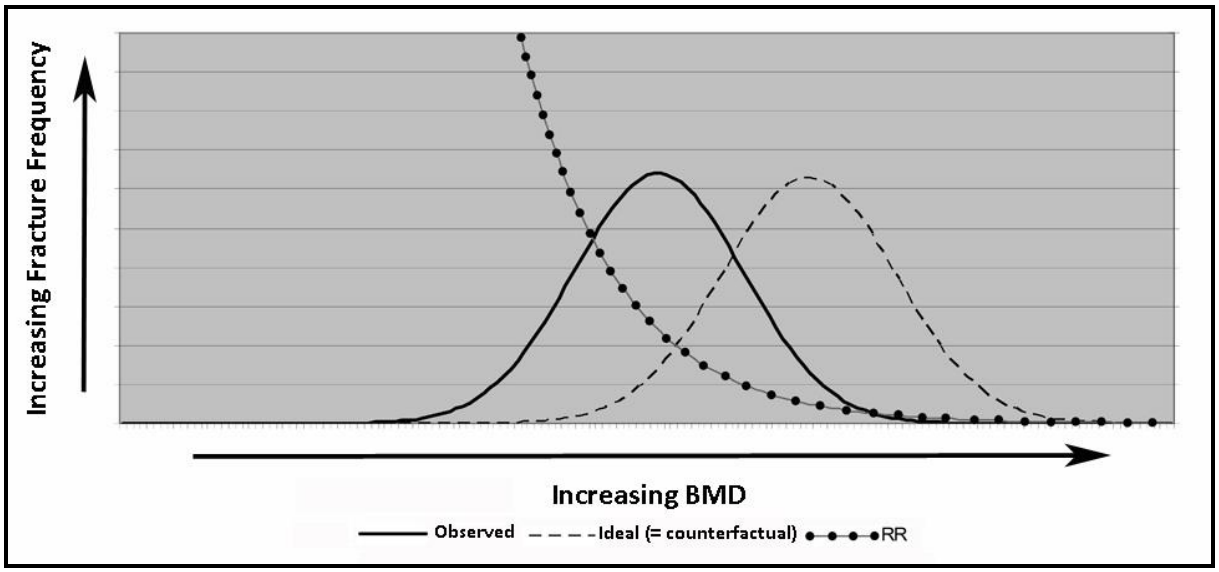

Figure 3.1 Counterfactual analysis in the Comparative Risk Assessment (CRA) methodology

In the CRA methodology, the incidence of fractures (outcome) for the observed distribution of the exposure variable (BMD) is compared to an ideal scenario where the population has an optimal level of BMD, conferring the minimum possible relative risk for fracture. BMD: bone mineral density. Adapted from Lennert Veerman, through personal communication.

The PAF represents the proportion of health burden that could be saved in the hypothetical scenario that the exposure to the risk factor was ideal (i.e *minimal*). In the present study, this leads to our main research question:

What proportion of the falls burden in the world could be avoided if all population had an ideal bone mineral density?

In order to answer this, the following steps were taken:

1) Definition of exposure variable: low bone mineral density (BMD)
2) Definition of the risk relationship between BMD and fractures by systematic review (SR)
3) Estimation of the global and regional levels of exposure by SR
4) Estimation of falls-related burden due to fractures
5) Estimation of PAFs of falls due to low BMD
6) Estimation of the global and regional health burden due to low BMD

Following the GBD framework, estimates of the health burden were done by country, world region, age group, gender and year (1990 and 2010). Estimates were limited to population 50 years and over due to the lack of valid longitudinal epidemiological data in premenopausal women and young male on the risk relationship between BMD and fractures, even after personal communication with the IOF in order to seek for valid non-published data. Other reasons to exclude younger population was the lower frequency of osteoporosis in premenopausal women (Odabasi, Turan et al. 2009) and young men and the high frequency of secondary causes of osteoporosis in this subgroup of population (e.g. glucocorticosteroid treatment, rheumatoid arthritis, Cushing disease, etc) (Peris, Guanabens et al. 2002; Odabasi, Turan et al. 2009), leading to altered bone quality, sarcopenia and increased risk of falls, factors that might be more relevant than low BMD in the fracture risk for younger population.

3.2 Constitution of the Osteoporosis Working Group

The project took into consideration networking efforts to analyse the results in the most suitable way, with the guidance from experts in osteoporosis epidemiology. An "Osteoporosis Work Group" (OWG) was created to develop a peer-reviewed assessment of the tools and the results of the SR, and ensure its consistency. The OWG was divided in "The Review Team" (RT) and the "Expert Leaders Group" (ELG), who were invited by formal letter. The ELG was constituted by public health experts enrolled in the GBD 2010 study, as well as world expert leaders in epidemiology of osteoporosis. All steps taken in the SR as well as provisional results were supervised by the MSK EG coordinators, the MSK EG leaders and members of the core team (CT) in the IHME (University of Washington), in order to provide feedback on unresolved issues and ensure the homogeneity within the GBD study (Table 3.1).

Table 3.1. Details and roles of the members of the "Osteoporosis Work Group"

Title	First_Name	Last_Name	Role	Institution	Country
Dr	**Lidia**	**Sanchez-Riera**	**MPO/RT**	**University of Sydney/Universitat de Barcelona**	**Australia/Spain**
Prof	Lyn	March	MSK EG leader	University of Sydney	Australia
Prof	Anthony	Woolf	ELG/MSK EG support leader	Universities of Exeter and Plymouth	United Kingdom
Dr	Damian	Hoy	MSK EG coordinator	University of Queensland	Australia
Dr	Emma	Smith	MSK EG coordinator	University of Sydney	Australia
Dr	Nicholas	Wilson	RT	University of Sydney	Australia
Ms	Monique	Macara	RT	University of Sydney	Australia
Dr	Cindy	Kok	RT	University of Sydney	Australia
Mr	Narainraj	Kamalaraj	RT	University of New South Wales	Australia
Dr	Yang	Li	RT	University of Sydney	Australia
Dr	Jian Shen	Chen	RT	University of Sydney	Australia
Dr	Carmen	Santos-Hernández	RT	SCNC & Universidad de Guadalajara	Cuba & Mexico
Dr	Lennert	Veerman	ELG	University of Queensland	Australia
Dr	Rosana	Norman	ELG	University of Queensland	Australia

Title	First_Name	Last_Name	Role	Institution	Country
Prof	John	Kanis	ELG	University of Sheffield	United Kingdom
Dr	Patricia	Clark	ELG	Faculty of Medicine UNAM	Mexico
Prof	Cyrus	Cooper	ELG	University of Southampton	United Kingdom
Prof	Philip	Sambrook	ELG	University of Sydney	Australia
Prof	Joan Miquel	Nolla	ELG/RT	Universitat de Barcelona	Spain
Prof	Kenneth	Saag	ELG	University of Alabama	United States
Prof	Theo	Vos	CT	University of Washington	United States
Prof	Stephen	Lim	CT	University of Washington	United States
Ms	Emily	Carnahan	CT	University of Washington	United States
Ms	Claire	Bryan-Hancock	IEG	Flinders University	Australia

MPO: main project officer. RT: The Review Team. MS KEG: Musculoskeletal Expert Group. SCNC: Sociedad Cubana de Nutrición Clínica y Metabolismo. ELG: Expert Leaders Group. UNAM: Universidad Nacional Autónoma de México. CT: core team. IEG: Injury Expert Group.

The RT was formed by 9 reviewers, guided by the main project officer (MPO) of the OWG, a rheumatologist with experience in osteoporosis research who was part of the GBD 2010 study working group. The MPO performed the screening of eligible studies from the SR, led the data extraction process, provided scientific evidence to ELG for team discussion when necessary, coordinated meetings and communication with member of the ELG, and led oral communications and manuscript writing related to the results of the study (Figure 3.2).

A series of workshops were undertaken within the RT and conducted by the MPO, in order to standardise and ensure the accuracy of the data extraction process and the correct application of the risk of bias tool (RoB). Any doubt or inconsistency appearing during raw data extraction, was consulted with the MPO directly to achieve consensus, who contacted the EGL or manuscripts' authors when required.

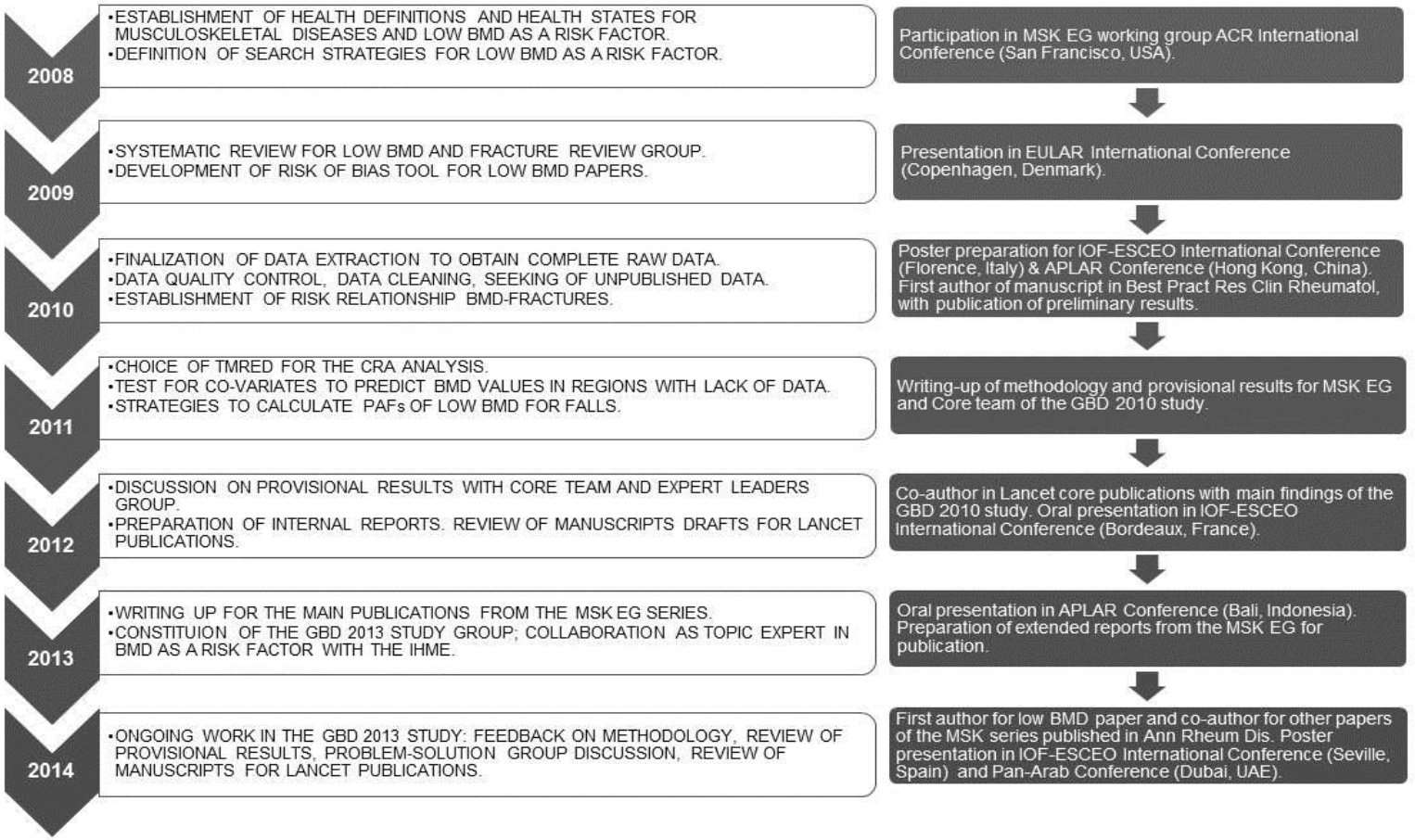

Figure 3.2. Flow chart of the contribution of the Main Project Officer for the Osteoporosis Working Group in the Global Burden of Diseases 2010 Study.

Figure on previous page represents: Contribution (left column) is paired with its concomitant scientific productions (right column) for each year. Full citations of posters, oral presentations and manuscripts can be found in chapter 10. BMD: low bone mineral density; MSK EG: musculoskeletal expert group; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; IOF: International Osteoporosis Foundation; ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; APLAR: Asia Pacific League of Associations for Rheumatology; GBD: Global Burden of Diseases.

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Duties of the ELG included Delphi exercises for consensus in search strategies and development of the RoB, agreement in the definition of the exposure variable, feedback on data extraction sheet format, networking to obtain non-published data, advice on the choice of the TMRED for the CRA analysis, feedback on RR for fractures obtained from previous meta-analysis and new data, critical approach of provisional results from the SR, and providing ideas on how to deal with missing data. This was undertaken by personal communication through email, phone, teleconferences and in group meetings during international conferences.

Finally, data on fracture incidence and prevalence obtained through the SR was coded separately and shared with the Injury Expert Group (IEG) in the GBD 2010 study (the search strategy for RR BMD-fractures captured a great amount of manuscripts with such information: the MPO classified the potential eligible articles by fracture type, data extraction was performed by the RT and all the information was shared with the IEG). The role of the MPO from the OPG in the literature review for fractures in the GBD 2010 study was reflected in the website of the IEG (https://sites.google.com/site/gbdinjuryexpertgroup/Home/literature-review#TOC-Literature-Review-Package). Worth to mention that data obtained from the OPG on fracture prevalence/incidence was not aiming to substitute the SR conducted by the IEG, but instead providing support on some tasks that were inevitably overlapping between both expert groups. Furthermore, the search strategy of low BMD as a risk factor for fractures was not originally designed to specifically capture articles on incidence and prevalence of fractures. Final management of fracture data provided by the OPG was entirely under the responsibility of the IEG and is beyond the scope of the present thesis.

3.3 Definition of the Exposure Variable: Low Bone Mineral Density

Low bone mineral density measured at femoral neck (FNBMD) by DXA in g/cm^2 was chosen as a continuous variable for the levels of risk of exposure. Reasons for selection of the technique and location are as follow:

1) Central DXA is the most validated and reliable technique to measure BMD, recommended as first choice for clinical and research purposes (WHO 1994; The International Society for Clinical Densitometry 2007).
2) More available epidemiological data is expected to be found with DXA than with other alternative and more recent techniques to measure BMD (QUS, pDXA, QCT, etc)
3) Measures with DXA are highly reliable and reproducible. Standard calibration methods are well established to ensure quality control of the DXA machines. The precision error (PE) is usually expressed as the coefficient of variation (CV), which is the ratio of the SD to the mean of the measurements. The ISCD has defined the acceptable ranges of PE in official positions (The International Society for Clinical Densitometry 2007).
4) Morbidity and mortality related to hip fracture (the osteoporotic outcome with the highest health burden) is better predicted when BMD is measured at FN rather than spine or forearm (Marshall, Johnell et al. 1996; Johnell, Kanis et al. 2005). Furthermore, measurement at the FN has been found to correlate well with vertebral and other osteoporotic fractures, and with any fracture (Johnell, Kanis et al. 2005).

5) Measurement of BMD at FN are more reliable than those performed at lumbar spine because of less interference of potential artefacts such as osteoarthritic changes and aortic calcification. Besides, BMD measurements at total hip have not proved to increase the predictive value of FN for fractures (Kanis, McCloskey et al. 2008).
6) The most solid epidemiological data available at the moment in regards to the RR of fracture related to BMD uses FNBMD (Johnell and Kanis 2006).

3.4 Description of the Systematic Review and Data Extraction Process

We performed a SR of Medline, Embase, CAB Abstracts, CINHAL, WHOLIS, and SIGLE databases using search strategies for risk factor levels of exposure (low BMD) and for risk relationship BMD-fracture. Inclusion criteria for both strategies were: population-based studies, publication from 1980 to 2009, BMD values in g/cm^2 measured by DXA at FN.

Search strategy 1. Risk factor levels of exposure (March 9th 2009)

mp. [mp=title, original title, abstract, name of substance word, subject heading word]

limit to (humans and yr="1980 - 2009")

(osteoporosis OR osteopenia OR osteopaenia OR bone mineral density OR radiolucency)

AND

(prevalen* OR inciden* OR cross-sectional OR cross sectional OR epidemiol* OR survey OR population-based OR population based OR population study OR population sample OR cohort OR follow-up OR follow up OR longitudinal OR regist* OR data collection)

AND

(GBD Countries MeSH MEDLINE) (Appendix 1)

Search strategy 2. Risk relationship BMD-fracture (March 9th 2009)

mp. [mp=title, original title, abstract, name of substance word, subject heading word]

limit to (humans and yr="1980 - 2009")

(osteoporosis OR osteopenia OR osteopaenia OR bone mineral density OR radiolucency)

AND

(fracture* OR risk)

AND

(GBD Countries SH EMBASE) (Appendix 1)

Exclusion criteria were: Exclusion criteria: *A:* Subsample not representative of the population (i.e: athletes); *B:* Non- population based studies (i.e: clinical based); *C:* No prevalence/incidence data (only applied for fracture data); *D:* Only concrete subtypes of osteoporosis assessed (i.e. steroid-induced OP); *E:* sample number <150. *F:* Reviews. In regions with limited data we also included other types of studies (e.g. non-population-based) as long as the sample was considered to be representative of the national population. No language exclusion criteria were set.

Retrieving of search results through databases was performed by one of the MSK EG coordinators. The next steps in the SR process from search results to final list of eligible studies were performed by the MPO of the OWG. All titles from SR were screened for eligibility. Eligible titles were then screened based on abstract content. Finally, full-text articles from eligible abstracts were retrieved in order to finish selection of eligible studies. Reference list of final eligible articles was screened as well as updates on search results from March 2009 to August 2010. When necessary, authors were contacted to voluntarily provide with raw data not available in the manuscripts.

3.4.1 Data extraction process

A database was developed and implemented in MS Excel and information was extracted from included studies into the following pre-determined fields for the exposure variable: region, country (for a complete list of countries in each GBD region, please refer to Appendix 1), year of publication, study type (cross-sectional, longitudinal, retrospective), sample size, population description, coverage, urbanicity (rural, urban or both), start year of data collection, last year of data collection, age group start, age group end, sex, ethnicity, DXA manufacturer, FN-specific CV, mean +/- SD of FNBMD value in g/cm^2. For risk relationship BMD-fractures, some additional fields were collected: follow-up duration (months), case definition for the outcome (i.e. fracture), outcome assessment method, parameter type for the effect size (i.e. relative risk, hazard ratio, odds ratio, etc), exposure unit for effect size (i.e. SD of BMD, absolute unit of BMD, osteoporosis WHO categories, etc) denominator, numerator (fracture cases), effect size value, lower and upper confidence interval

(CI), percentage of the CI, p value, outcome rate in the exposed group, outcome rate in the non-exposed group (applicable if the exposure unit was categorical such as number of SD, quartiles, etc), mean exposure value in non-fracture cases (i.e. mean BMD, mean T score, etc), mean exposure value in fracture cases, reference population (relevant if T or Z scores were used), presence and identification of adjustments (age, ethnicity, BMI, etc).

All mean FNBMD and SD values with different DXA manufacturers (mainly Hologic®, Norland® and Lunar®) were standardized by an international conversion formulas to standardized mean FNBMD (sFNBMD) and SD (sSD) (Lu, Fuerst et al. 2001; Binkley, Kiebzak et al. 2005) (Table 3.2). Personal communication with the authors of such standardization equations (Lu, Fuerst et al. 2001) was established to ensure no updates in such conversion formulas existed and their correct application in our study.

Table 3.2. International Conversion Formula to Standardize BMD Tests from Different Manufactures

Manufacture		Equation
Generic		
	sBMD	= a + (b * X)
	sSD	= (b * SD)
Hologic		
	sBMD	= +0.019 + (1.087 x Hologic BMD)
	sSD	= 1.087 x Hologic SD
Lunar		
	sBMD	= -0.023 + (0.939 x Lunar BMD)
	sSD	= 0.939 x Lunar SD
Norland		
	sBMD	= +0.006 + (0.985 x Norland BMD)
	sSD	= 0.985 x Norland SD

Conversion formulas for FNBMD (Lu, Fuerst et al. 2001; Binkley, Kiebzak et al. 2005). sBMD: standardized Bone Mineral Density; sSD: Standardized Standard Deviation.

3.4.2 Data quality control

All included studies were assessed for bias using a modified version of a validated RoB tool (Appendix 2) (Hoy, Brooks et al. 2012) developed for prevalence studies, and adapted for low BMD (Sanchez Riera, Wilson et al. 2010). First step in the creation of this BMD-specific RoB tool was the development of the first draft by the MPO after performing literature review on the topics included when required. Next, a series of Delphi exercises took place within MSK EG and the EGL in the OWG until achievement of the provisional final version. An initial exercise with around 20% of

eligible studies chosen randomly was undertaken within the RT to test the applicability of the tool during data extraction process, and feedback was provided in order to improve the tool. Group workshops were carried out in the RT to discuss controversies and guarantee homogeneity of criteria among reviewers. Assessment items in the RoB tool for low BMD included: 1) definition of the anatomical location of the BMD measurement, 2) definition of measured outcome (fracture), 3) reliability of the BMD measurement, 4) reliability of the outcome measurement, 5) representativeness of the national population, 6) quality of the sample frame, 7) randomization, 8) non-response bias, 9) adjustment for confounding factors, 10) length of the follow-up period, 11) adequacy of follow-up cohort, 12) selection bias, and 13) overall risk of bias. Items 2, 4, 9-11 were only applicable to papers with fracture risk data related to low BMD. Risks of bias for each item were *Low*, *Moderate* (only some items), *High* and *Unclear* taking into account established and peer-reviewed criteria attached with the RoB tool for all the reviewers.

Regular quality checks were done by the MPO with the aim to ensure accuracy of the data. Besides, a random sample of one third of the studies was doubled reviewed by the MPO to check precision in data extraction and right application of the RoB tool.

Generalized linear models were used to assess whether there were significant differences in mean sBMD between overall bias groups. Analytical weights were used when dealing with the data containing averages. Potential correlations within a specific study were taken into account by specifying the estimator's "cluster clustvar" option in Stata™ version 11.1.

Finally, a systematic data cleaning process was performed to identify duplicated data and inconsistencies in the values. When necessary, full-text review or contact with the authors was carried out. Final set of raw clean data was provided to the CT in the University of Washington. As data were available for only selected country-time periods, the mean sBMD and sSD was estimated separately for all country-time periods using DisMod-MR, a Bayesian meta-regression tool developed specifically for GBD 2010 (Vos, Flaxman et al. 2012). The model included fixed effects for study-specific covariates, and random effects by GBD super-region, region, and country. Estimates for males and females in 5-year groups for population 50 years and over for 1990, 2005, and 2010 were produced.

3.4.3 Missing data

A screening of the dataset results from the SR helped to identify those regions and countries where there was insufficient data or data obtained was uncompleted for the purposes of this project, as shown in Figure 4.2 of *Results*. In such cases, authors were contacted through email and asked to voluntarily provide the data in the right format or to facilitate non-published data.

Using DisMod-MR, study-specific covariates accounted for inconsistencies in the raw data; for example, data that were subnational (rather than nationally representative), or data that were collected in a non-gold-standard way (e.g. non-population based). National-level covariates could be used in the model to inform the global and country-level trends, and were not study-specific; lag-distributed income per capita, mean body mass index (BMI), and availability of milk based on the Food and

Agriculture Organization of the United Nations disappearance data (imports plus local production minus exports) were tested. Even though there are other well-known predictors of low BMD, the analysis was limited to variables with good national data within the GBD 2010 project. For example, available estimates for physical activity only included solid data from 2005 period with very few surveys pre-2000. Raw data introduced in Dismod-MR did not allow production of estimates by ethnicity or race breakdown either, although regional effects were considered to account for part of that. Other risk factors such as alcohol or smoking gave ambiguous results, and after consensus with ELG, their inclusion in the model was ruled out given that their impact in the BMD distribution at a population level was thought to be rather small.

3.5 Relative Risk Assessment: Low Bone Mineral Density as a Risk Factor for Fractures

3.5.1 Risk Factor Effect Size

Defining the right relationship between low BMD and fracture risk was a key step in our methodology.

Few studies in search strategy 2 met inclusion criteria (i.e. population-based studies using FNBMD measured by DXA). Given the major relevance of one existing meta-analysis (MA) published in 2005 (Johnell, Kanis et al. 2005), a consensus was reached with the ELG to screen for high quality data after the abovementioned MA. Hence, only longitudinal studies with long-follow up periods to enable fracture risk assessment published after 2005 were considered. As it will be shown later on (refer

to 4.1 Results from Systematic Review), a very little number of studies met such criteria. Moreover, the RRs of fracture related to FNBMD was comparable to those found in the MA, with a total sample size which was clearly inferior to that from the MA, and with important heterogeneity among studies in terms of study design, location of BMD measurement and fracture outcome (e.g. some studies measured morphometric vertebral fractures while other only considered clinical vertebral fractures). For all this, no need to update fracture risk data from the MA was considered to be required or relevant for the results.

Thus, our estimates on the RR of FNBMD for fractures were based on this crucial meta-analysis (Johnell, Kanis et al. 2005), which has become the cornerstone of the most widely accepted fracture prediction tool around the world (i.e. FRAX®) (Cauley, El-Hajj Fuleihan et al. 2011). Such MA studied 9891 men and 29,082 from 12 population-based cohorts from Western Europe, USA, Canada, Japan and Australia. The mean follow-up period was 16.3 years, with a total of 168,366 person-years. Authors reported age- and gender-adjusted RRs for hip and non-hip fractures attributable to BMD for population 50 years and older.

The estimates of the gradient of risk (RR/SD) for FNBMD Z-scores, based on the combined data for men and women, were obtained from the authors of the MA (Johnell, Kanis et al. 2005) by personal communication. In the MA, Z-scores were established within each study population separately, which made the RRs dependent on the spread within the study population. For our purposes this was undesirable, and therefore the ‘relative’ RR/SD values were converted to ‘absolute’ RR/0.1g/cm2 values (Table 3.3 Relative Risk (RR) for hip and non-hip fractures for each 0.1g/cm2

decrease in bone mineral density) using a weighted average of the spread in FNBMD values for the populations that were represented in the MA, as they were estimated in the DisMod-MR output, and so derived risk estimates for men and women separately by 5-year age group.

Table 3.3 Relative Risk (RR) for hip and non-hip fractures for each 0.1g/cm2 decrease in bone mineral density

	Age	Non-hip fractures			Hip fractures		
Males		Mean	LCI	HCI	Mean	LCI	HCI
	50-54	1.152	1.058	1.254	2.603	2.042	3.319
	55-59	1.183	1.104	1.268	2.421	1.978	2.961
	60-64	1.215	1.147	1.286	2.282	1.938	2.689
	65-69	1.249	1.189	1.311	2.177	1.914	2.478
	70-74	1.297	1.238	1.357	2.100	1.897	2.324
	75-79	1.338	1.279	1.402	1.921	1.781	2.072
	80+	1.371	1.302	1.444	1.730	1.627	1.840
Females							
	50-54	1.158	1.061	1.265	2.697	2.096	3.470
	55-59	1.201	1.114	1.296	2.629	2.109	3.278
	60-64	1.237	1.162	1.317	2.466	2.062	2.951
	65-69	1.286	1.216	1.358	2.412	2.084	2.792
	70-74	1.342	1.274	1.413	2.315	2.064	2.596
	75-79	1.398	1.327	1.475	2.118	1.942	2.311
	80+	1.438	1.355	1.526	1.878	1.750	2.016

(Table on previous page) Values are relative risk for fracture (RR) per each 0.1 unit of bone mineral density (BMD) decrease at femoral neck (FNBMD). Units of BMD are g/cm^2. LCI: lower 95% confidence interval; HCI: high 95% confidence interval. Using original data from Johnell et al 2005 (Johnell, Kanis et al. 2005) through personal communication.

3.5.2 Definition of the Theoretical Minimum Risk Exposure Distribution

Defining the theoretical minimum risk exposure distribution (TMRED) for our PAFs estimations was one of the most difficult decisions taken in this project. We compared three possible scenarios:

1) Initially, we adopted the ***young white female reference from NHANES III*** (Looker, Wahner et al. 1998) as the current recommended international reference standard for definition of osteoporosis using FNBMD measured by DXA (Kanis, McCloskey et al. 2008; The International Society for Clinical Densitometry. 2007). Controversies appeared in regards to this approach. The reason behind is that in the GBD framework, risk factor analysis focuses on *modifiable* risk factors. The TMRED should be theoretically possible at the population level and supported by convincing epidemiological evidence of a continuous risk reduction to that exposure distribution (Ezzati, Hoorn et al. 2011). Hence, to support such approach, scientific evidence proving that women could exhibit similar FNBMD than men in the presence of an ideal health should have been obtained. This could have been relevant from an individual scope, but rather unrealistic at a population level, given than BMD in any age group, similarly to other biological parameters such as height or

body muscle mass, follows a normal distribution in both sexes, but exhibits, physiologically, higher values in men than in women. Besides, females show faster rates of bone loss after menopause compared to males (Jones, Nguyen et al. 1994; Burger, de Laet et al. 1998; Yoshimura, Kinoshita et al. 2002). Furthermore, preliminary calculations of PAFs of BMD for fractures gave *negative* values in males from few world regions both for hip (Figure 3.3) and non-hip fractures (Figure 3.4). Such results were not plausible within the CRA analysis, as it would have meant that the risk factor exposure (i.e. low BMD) in this subgroup was protective against the analysed outcome (i.e. fractures).

2) The next tested scenario was drawn from the TMRED set at the ***sex-specific young white reference from NHANES III*** (Looker, Wahner et al. 1998). This approach solved the issue of finding negative PAFs for males. However, it could still capture non-modifiable declines of FNBMD due to age. Independent literature review on this topic was carried out by the MPO, and reviewed by the CT and the ELG. Few longitudinal studies (Burger, de Laet et al. 1998; Cauley, Lui et al. 2009) were found demonstrating that a small percentage of elderly could maintain their bone mass over the time in the absence of risk factors for osteoporosis. However, the extents to which the differences in BMD observed by age were modifiable were not certain, and we didn't find definitive evidence showing that individuals could maintain their young peak bone mass as they age. In contrast, longitudinal cohorts have shown a clear bone loss associated with ageing at a population level in different genders, ethnicities and world regions (Steiger, Cummings et al. 1992; Jones, Nguyen et al. 1994; Burger, de Laet et al. 1998; Yoshimura, Kinoshita et al. 2002; Kaptoge, Reid et al. 2007).

3) Finally, we compared the two previous scenarios with a third approach using an ***age- and sex-specific TMRED from NHANES III*** (Looker, Wahner et al. 1998) in order to remove the non-modifiable effect of age and sex from the theoretical achievable optimal level of BMD. For the choice of the concrete percentile within each gender and age group (e.g. 75th percentile, 95th percentile, etc) the following considerations were made: First, there is an evidence of a continuous risk relationship between BMD and fracture risk up to very high levels (i.e. gradient of risk keeps decreasing up to Z scores as high as +4 in the MA used for our RR BMD-fractures) (Johnell, Kanis et al. 2005), supporting the choice of a high sex- and age-specific percentile from NHANES III for the TMRED. Second, a significant correlation of BMD with genetic factors has been found in twin studies, which remains independent after adjusting for other biometric parameters and environmental factors, despite it tends to attenuate with age (Pocock, Eisman et al. 1987; Slemenda, Christian et al. 1991; Harris, Nguyen et al. 1998). Based in such consideration, a TMRED set at the 99th or 95th percentile could not be achievable for most of the population even in the absence of risk factors for low BMD. However, a feasible way to map such findings into the NHANES III BMD distribution in order to help with the percentile choice for the TMRED was not found. Several group discussions were held with public health experts from the ELG and epidemiology and statistics experts from the CT to solve this issue. The final decision was to take the 90th percentile as the threshold for an *achievable* optimal level of BMD. Albeit arbitrary, this threshold seemed realistic without being too conservative.

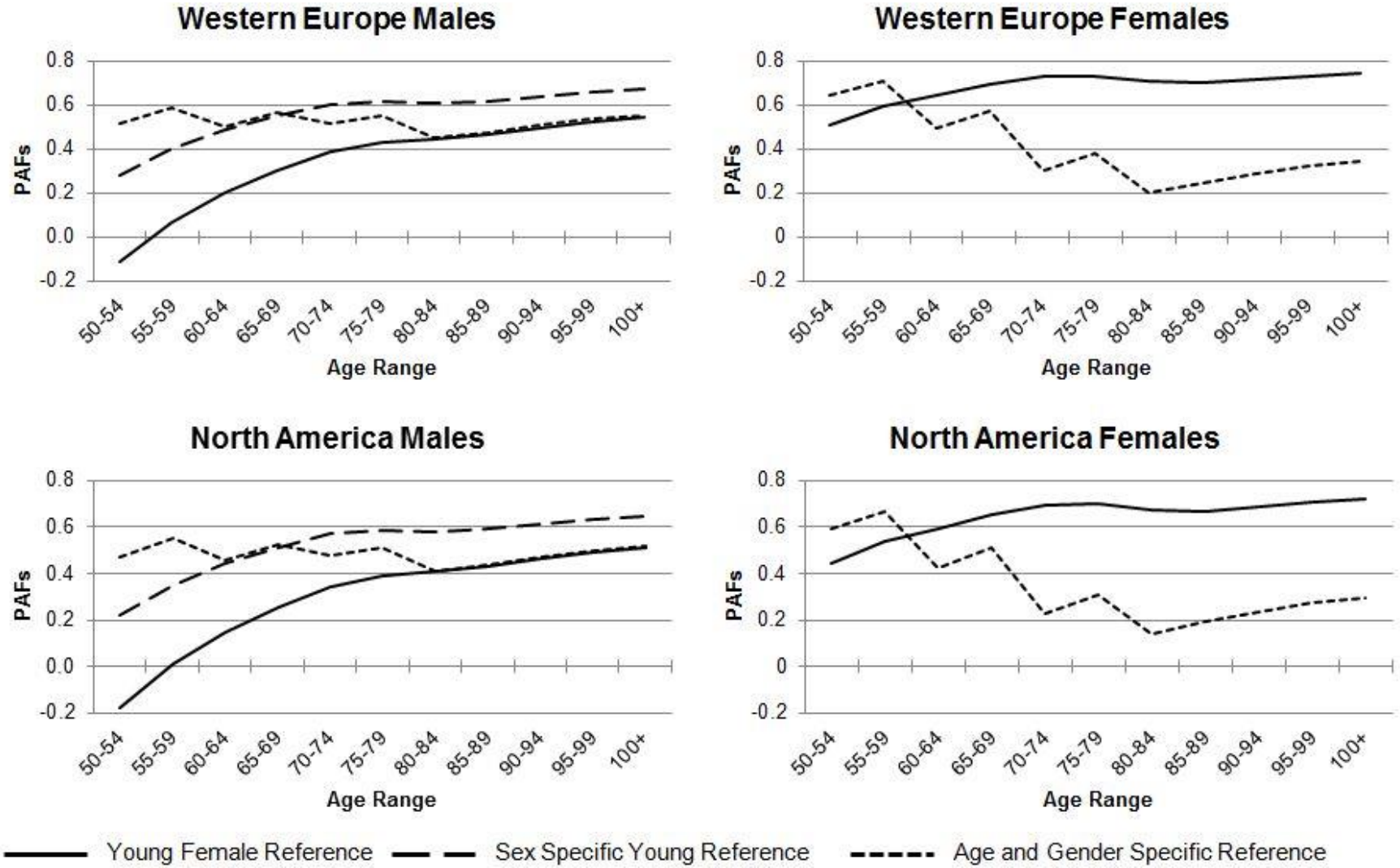

Figure 3.3. Different approaches for the Theoretical-Minimum-Risk Exposure Distribution (TMRED) to calculate the Population Attributable Fractions (PAFs) of low bone mineral density at femoral neck (FNBMD) for hip fractures.

Figure on previous page shows results for 2005 for hip fracture estimates. Western Europe and North America High Income were chosen for being word regions with high proportion of data points within the worldwide estimates. As shown in the figure, the use of a female young reference as the TMRED for both sexes led to negative PAFs for males. The use of a sex-specific young reference followed the same tendency with age than the previous approach, although values of PAFs in males were higher when using male-specific young reference. Finally, with an age- and sex-specific reference, PAFs were quite homogenous over the age groups for males, while they tended to decline with the age in females. Note that the curves of PAFs using young female reference and sex-specific young reference overlap in females.

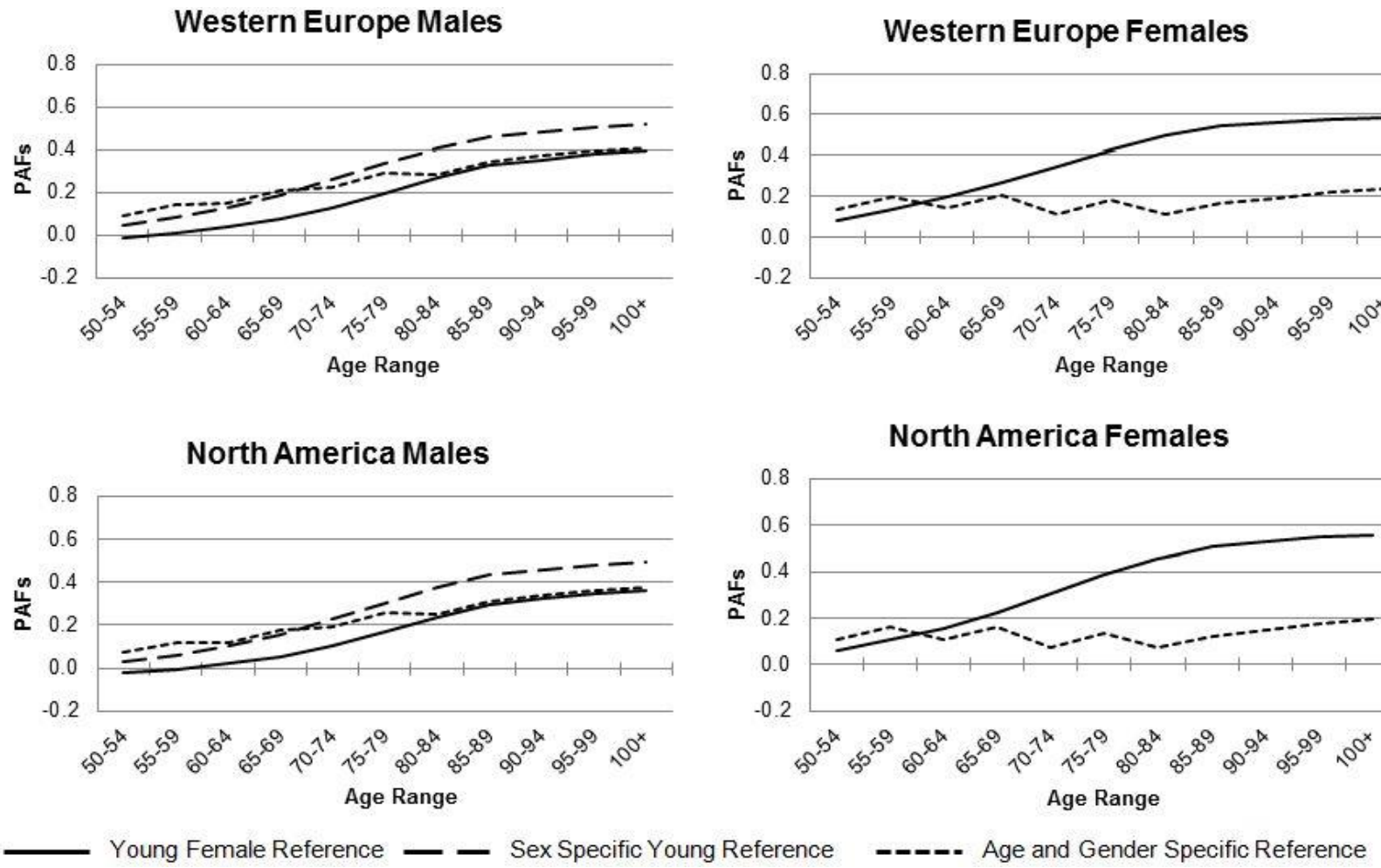

Figure 3.4. Different approaches for the Theoretical-Minimum-Risk Exposure Distribution (TMRED) to calculate the Population Attributable Fractions (PAFs) of low bone mineral density at femoral neck (FNBMD) for non-hip fractures.

Figure on previous page shows results for 2005 for non-hip fracture estimates. Western Europe and North America High Income were chosen for being word regions with high proportion of data points within the worldwide estimates. For non-hip fractures, PAFs calculated with an age- and sex-specific reference tended to increase from younger to older ages in both sexes, although the increase was more marked in males than in females, being PAFs in males around two-fold the PAFs in females except for age groups 50-54 and 55-59, where PAFs were higher for women. Note that the curves of PAFs using young female reference and sex-specific young reference overlap in females.

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To assist with the choice of the TMRED among the three possible approaches, comparative exercises were performed by public health experts from the University of Queensland, shown in Figure 3.3 and Figure 3.4. Finally, the sex and age-specific 90th percentile of FNBMD (after standardization) (Lu, Fuerst et al. 2001) from whites in NHANES III (Looker, Wahner et al. 1998) was used as the TMRED (Table 3.4) for PAFs calculations. The SD of the TMRED was estimated based on the relationship between means and SDs from a regression of all studies in the final dataset that measured means and SDs of FNBMD.

Table 3.4 Theoretical-minimum-risk exposure distribution (TMRED) for males and females 50 years and over.

	Age	Mean sBMD	SD
Females	50-59	1.00	0.14
	60-69	0.92	0.14
	70-79	0.84	0.13
	80+	0.78	0.13
Males	50-59	1.09	0.16
	60-69	1.06	0.16
	70-79	1.02	0.16
	80+	0.98	0.16

Values are expressed in g/cm^2 and correspond to the age- and sex-specific 90th percentile of the mean FNBMD from whites in NHANES III (Looker, Wahner et al. 1998) after internationally recognized standardization (Lu, Fuerst et al. 2001). sBMD: standardized bone mineral density; SD: standard deviation

3.6 Health Burden of Falls Attributable To Low Bone Mineral Density

3.6.1 Mortality related to low bone mineral density

Mortality associated with low BMD was estimated through the calculation of deaths due to osteoporotic fractures in population 50 years old and over. As explained previously, mortality data in the GBD 2010 study was obtained from different sources; most importantly from national vital registries and in-hospital data (Lozano, Naghavi et al. 2012) (refer to section 1.8: Context of the Thesis Project: The Global Burden of Diseases 2010 Study (The GBD 2010 study). For attributing deaths to low BMD the difficulty was that deaths were categorised according to cause of injury (i.e. falls), not nature of injury (i.e. fracture), and low BMD or osteoporosis was not generally coded as a cause. Fractures can be found as a consequence of many injuries such as road injury, assault or natural disasters. For the purposes of this analysis, estimates were restricted to fractures due to accidental falls, where we expected most osteoporotic fractures to be coded. We used official nationwide hospital data with double coding (i.e cause and nature of injury) from Brazil (Ministry of Health (Brazil). 2006-2009), Canada (Canadian Institute for Health Information.1994-2009), Mexico (Ministry of Health (Mexico). 2000-2009) and the United States (Healthcare Cost and Utilization Project. 2003-2008) to estimate the fraction of in-hospital deaths from falls that involved hip and vertebra fractures.

Those with a mention of concurrent head or internal injury were excluded, as they would potentially interfere in the mortality outcome directly attributed to the fracture.

Other fracture types were excluded as these were considered less likely to lead to death, as supported by an analysis of the Australian mortality database (http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3303.0Main+Features12003?OpenDocument). Among those inpatient deaths where the primary cause for admission was a fall, a large fraction, especially at older ages, had a hip fracture. Only a small proportion of deaths associated with vertebral fracture were not also associated with a hip fracture (non-hip vertebra fractures) (Table 3.5). As this was the only data source used to determine the fraction of deaths from falls due to hip fracture or vertebra fracture, it was necessary to apply these age and sex-specific proportions to falls to every country.

Table 3.5. Hip fractures and non-hip vertebra fractures as a fraction of all in-hospital deaths attributable to falls.

Sex	Age	Hip Fracture (%)	Non-hip Vertebra Fracture(%)
Females	50-59	61.6	2.6
	60-69	73.2	1
	70-79	79.4	0.6
	80+	82.5	0.5
Males	50-59	46	8
	60-69	67.5	4.6
	70-79	79.8	0.9
	80+	84.2	0.4

Percentages express the fraction of in-hospital deaths from falls that involve hip fractures and non-hip vertebra fractures (deaths from vertebral fractures that occur without hip fracture). Calculated with in-patient hospital data from Brazil (Ministry of Health (Brazil). 2006-2009), Canada (Canadian Institute for Health Information. 1994-2009), Mexico (Ministry of Health (Mexico). 2000-2009) and the United States (Healthcare Cost and Utilization Project. 2003-2008; National Center for Health Statistics, Centers for Disease Control and Prevention, US Census Bureau. 1979-2009)

The ICD-9 and ICD-10 codes used for falls were those coding for *accidental* or *unintentional* falls with some important exclusions such as road accidents and can be found in Appendix 3. Of relevance is the fact that some of the falls codes were likely to include both high energy and low energy injuries (e.g. E884 *Other fall from*

one level to another), and therefore fractures due to some of those falls would have not been classified as *fragility fractures* or *osteoporotic* (i.e. fractures occurring due to falls from standing height). Nevertheless, the differentiation between high energy and low energy injuries in such cases was virtually not possible, and the inclusion of all falls types in Appendix 3 was considered necessary in order not to lose any potential burden due to low BMD. Application of the RRs from Table 3.3 (derived for *osteoporotic* fractures) were still considered to be acceptable for all falls codes for the following reasons: First and most important, the risk relationship between BMD and fractures for *any fracture* was only mildly different to that for *osteoporotic fracture* in the MA used to derive the RRs from Table 3.3. In particular, RR/SD in BMD decrease (FNBMD of young white females from NHANES III) for males and females combined was 1.46 (95% CI: 1.40-1.52) *versus* 1.56 (95% CI: 1.49-1.64) for any fracture and osteoporotic fracture, respectively. Second, creating a new subset of RR BMD-fractures for high energy falls would have been too tedious, due to the possible different weight of BMD in the fracture occurrence for each type of fall and the lack of enough high quality epidemiological data to run such analysis. And finally, the use of the RRs in Table 3.3 allowed to separate the estimations for hip and non-hip fractures, which was considered relevant due to the major health burden due to hip fractures compared with other fracture types and the higher relative weight of low BMD in the fracture event in comparison to other locations.

3.6.2 Disability related to low bone mineral density

Disability from unintentional falls (Appendix 3) was estimated by the nature of associated injury and therefore the short and long-term disability was estimated for

fractures by site. Estimations of the disability related to falls were the responsibility of the IEG in the GBD 2010 study, and data was shared with the OPW and the CT in order to calculate the proportion of that disability attributable to low BMD. In brief, injury causes (including falls) in the GBD 2010 study were analysed using five steps (Vos, Flaxman et al. 2012). First, household surveys and hospital discharge data (hospital in-patient and emergency department data) were analysed using DisMod-MR for each external cause to generate estimates of incidence by age, sex, country, and year. Second, hospital data from 28 countries that had dual coding of discharges by external cause and nature of injury was analysed. Third, for each nature of injury probability of individuals developing long-term functional impairment was estimated through follow-up data from selected studies. Fourth, DisMod-MR was used to estimate the prevalence of individuals in the population who were likely to have functional limitation because of a previous injury. And finally, fifth, YLDs due to prevalent cases of long-term injury were attributed back to external causes in proportion with the contributions of these causes (e.g. falls) to every type of injury (e.g. fractures).

Table 3.6 shows final lay descriptions and disability weights (DWs) for each fracture type. Summary of the methods used to calculate DWs can be found in section 1.8 *Context of the Thesis Project: The Global Burden of Diseases 2010 Study (The GBD 2010 study*), and detailed methodology to generate DWs and lay descriptions have been reported elsewhere (Salomon, Vos et al. 2012).

Table 3.6 Disability Weight (95% Uncertainty Intervals) and Lay Description for each fracture type

Type of Fracture	Lay description	Disability weight (95% UI)
Fracture of clavicle, scapula or humerus: short or long term, with or without treatment	Has a broken shoulder bone, which is painful and swollen. The person cannot use the affected arm and has difficulty with getting dressed.	0.053 (0.033-0.080)
Fracture of face bone: short or long term, with or without treatment	Has a broken cheek bone, broken nose, and chipped teeth, with swelling and severe pain.	0.173 (0.111-0.257)
Fracture of foot bones: short term with or without treatment	Has a broken foot bone, which causes pain, swelling, and difficulty walking.	0.033 (0.019-0.053)
Fracture of foot bones: long term with or without treatment	Had a broken foot in the past that did not heal properly. The person now has pain in the foot and Has some difficulty walking.	0.033 (0.019-0.052)
Fracture of hand: short term with or without treatment	Has a broken hand, causing pain and swelling.	0.025 (0.013-0.043)
Fracture of hand: long term without treatment	Has stiffness in the hand and a weak grip.	0.016 (0.008-0.028)

Type of Fracture	Lay description	Disability weight (95% UI)
Fracture of neck of femur: short term with or without treatment	Has broken a hip and is in pain. The person cannot stand or walk, and needs help washing, dressing, and going to the toilet.	0.308 (0.205-0.439)
Fracture of neck of femur: long term with treatment	Had a broken hip in the past, which was fixed with treatment. The person can only walk short distances, has discomfort when moving around, and has some difficulty in daily activities.	0.072 (0.047-0.105)
Fracture of neck of femur: long term without treatment	Had a broken hip bone in the past, which was never treated and did not heal properly. The person cannot get out of bed and needs help washing and going to the toilet.	0.388 (0.261-0.532)
Fracture other than neck of femur: short term with or without treatment	Has a broken thigh bone. The person has severe pain and swelling and cannot walk.	0.192 (0.121-0.280)
Fracture other than neck of femur: long term, without treatment	Had a broken thigh bone in the past, which was never treated and did not heal properly. The person now has a limp and discomfort when walking.	0.053 (0.035-0.079)

Type of Fracture	Lay description	Disability weight (95% UI)
Fracture of patella, tibia or fibula or ankle: short term with or without treatment	Has a broken shin bone, which causes severe pain, swelling, and difficulty walking.	0.087 (0.055-0.127)
Fracture of patella, tibia or fibula or ankle: long term with or without treatment	Had a broken shin bone in the past that did not heal properly. The person has pain in the knee and ankle, and has difficulty walking.	0.070 (0.047-0.102)
Fracture of pelvis: short term	Has a broken pelvis bone, with swelling and bruising. The person has severe pain, and cannot walk or do daily activities.	0.390 (0.257-0.545)
Fracture of pelvis: long term	Had a broken pelvis in the past and now walks with a limp. There is often pain in the back and groin, and when urinating and sitting for a long time.	0.194 (0.132-0.272)
Fracture of radius or ulna: short term with or without treatment	Has a broken forearm, which causes severe pain, swelling, and limited movement.	0.065 (0.040-0.101)

Type of Fracture	Lay description	Disability weight (95% UI)
Fracture of radius or ulna: long term without treatment	Had a broken forearm in the past that did pain and limited movement in the elbow and wrist. The person has difficulty with daily activities such as dressing.	0.050 (0.032-0.075)
Fracture of skull: short or long term, with or without treatment	Has a broken skull, but does not have brain damage. The broken area is painful and swollen.	0.073 (0.046-0.109)
Fracture of sternum or fracture of one or two ribs: short term with or without treatment	Has a broken rib that causes severe pain in the chest, especially when breathing in. The person has difficulty with daily activities such as dressing.	0.150 (0.098-0.215)
Fracture of vertebral column: short or long term with or without treatment	Has broken back bones and is in pain, but still has full use of arms and legs.	0.132 (0.085-0.195)

UI: Uncertainty Interval. Adapted from Salomon et al 2012(Salomon, Vos et al. 2012). Fracture of neck of femur accounts for *hip fracture* estimates.

To understand the relative weight of the fractures burden for the YLDs calculation, a comparison with other GBD causes (*sequelae*) is a helpful exercise (Appendix 4). The short-term DW resulting from hip fracture (i.e. 0.308) can be compared, for example, to the DWs from severe heart failure (0.186), short-term disability from severe traumatic brain injury (0.235), or a severe major depression episode (0.655). Similarly, the long-term disability resulting from hip fracture after treatment (0.072) can be weighed against those from amputation of one leg after treatment (0.021), severe Parkinson disease (0.549) or moderate dementia (0.346). In general, DWs associated to causes with currently no or little healing treatment (e.g. dementia, multiple sclerosis, Parkinson disease, etc) and mental and drug abuse disorders scored the highest in the DWs list.

To calculate the YLDs due to low BMD, the RR of BMD for hip fracture (Table 3.1) was applied to the YLD estimates for fracture of hip due to falls sub-cause (Table 3.6). The RR of low BMD for non-hip fracture (Table 3.1) was applied to YLD estimates for all other fracture sites (Table 3.6).

3.6.3 Attributable Burden Estimation Method

The attributable health burden due to low BMD was calculated by comparing the observed distribution of sFNBMD to the counterfactual distribution for each age, sex, year, and cause according to the following formula:

$$PAF = \frac{\int_{x=0}^{m} RR\,(x)P(x)dx \; - \; \int_{x=0}^{m} RR\,(x)P'(x)dx}{\int_{x=0}^{m} RR\,(x)p(x)dx}$$

where *RR(x)* is the relative risk at exposure level *x*, *P(x)* is the population distribution of exposure, *P'(x)* is the counterfactual distribution of exposure, and *m* the maximum exposure level.

Resulting PAFs of BMD for fractures were, then, applied to the YLDs of fractures for falls. For mortality estimations of the burden, PAF's were applied to the fractions of falls-related deaths due to hip and non-hip vertebra fracture exposed in Table 3.5.

3.7 Ethical Aspects

Ethical requirements in the GBD 2010 study were under the scope of the core team (CT) from the University of Washington.

As per the present work, details on the type of research were provided to the Northern Sydney Local Health District Human Research Ethics Committee, which declared the study as being exempt from approval by the Human Research Ethics Committee.

4 RESULTS

4.1 Results from Systematic Review

The flowchart for the systematic review is shown in Figure 4.1. There were 130 eligible articles (Appendix 5), with a total of 860 data points from 49 countries and 17 world regions (Figure 4.2). Number of data points was very diverse among world regions, with 4 out of the 21 world regions with no data at all. Data on population levels of BMD was presumably more robust for the 2010 time point, as number publications clearly increased with the years from 1990 to 2010 (Figure 4.3).

The RoB did not prove predictive value for sFNBMD for the overall risk of bias at any age group in men or women (Table 4.1). Selection bias was clearly heterogeneous among studies, considered *Low* (34% of studies) when most recruited subjects were included, *Moderate* (38%) when those under diseases or therapies with potential effect on bone metabolism were excluded, and *High* (28%) when subjects with prior fractures were excluded. The distribution was not remarkably different when percentages were analysed by sex group (Figure 4.4). Subgroup analysis based on selection bias was undertaken under the hypothesis of being one of the key sources of potential bias. However, no significant differences in sFNBMD values were found between *High* risk of bias and *Low* risk of bias for both males and females; sFNBMD was significantly higher for *Moderate* risk when compared to *Low* risk, in males only ($p=0.042$) (Figure 4.5). At the view of these results, no differential weight was given to data depending on the RoB category, and all sFNBMD values were included in the final analysis with the same relative weight of 1.0 (that is, all studies were attributed the same *importance* based on the results of the RoB tool).

None of the covariates tested in DisMod-MR (income per capita, mean BMI, and availability of milk) demonstrated a significant improvement in the predictive ability of the model and were therefore not included.

As per the results of the second search strategy (*risk factor-disease relationship*) (Figure 4.1), very few articles were found to have a potential impact on the RRs derived from the MA (Johnell, Kanis et al. 2005) used in the PAF calculations. After focusing in those ones published after such MA, taking out those from previous cohorts used in the latter, and selecting only longitudinal population-based studies, only a very short list of articles was considered (Table 4.2). The data was shared with the ELG, which in view of the relative small sample size of the studies all together and the *comparable* risk relationship BMD-fractures of the individual studies to those ones observed previously, recommended no further updates of the RRs used for the CRA analysis.

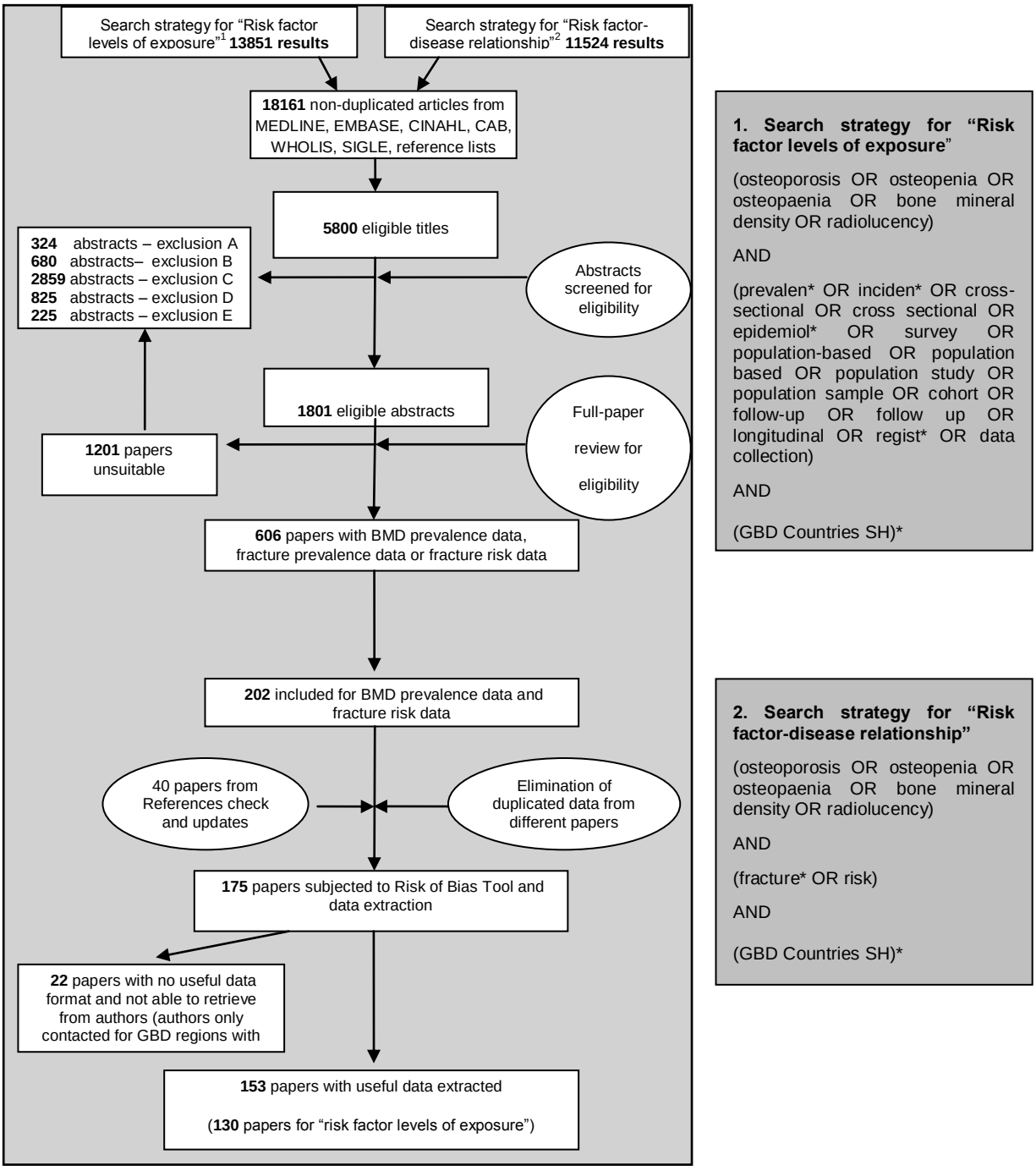

Figure 4.1. Flowchart for the Systematic Review Process

LEFT: Flowchart for the systematic review process. RoB: Risk of Bias. **RIGHT**: Search strategies for BMD as the exposure variable and BMD as a risk factor for fractures.Review process included all published studies until February 2008 with updates up to August 2010* The whole list of the world countries (Appendix 1) was used as Subject Headings in Medline, Embase, Cinhal, and CAB abstracts. Exclusion criteria: A: Subsample not representative of the population (i.e: athletes); B: Non- population based studies (i.e: clinical based); C: No prevalence/incidence data; D: Only subtypes of osteoporosis assessed (i.e. steroid-induced OP); E: sample number <150. F: Reviews. BMD: bone mineral density; GBD: Global Burden of Diseases.

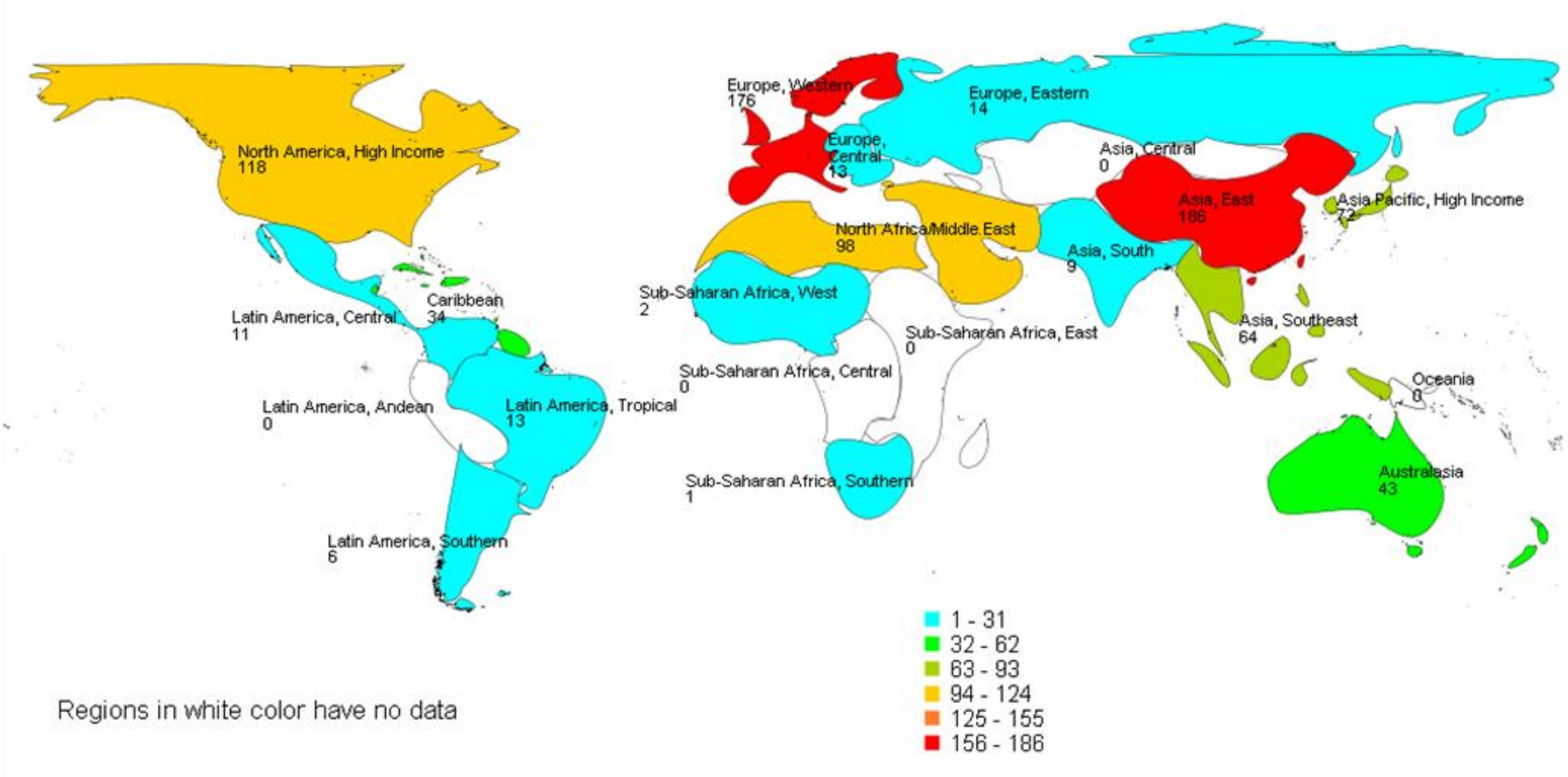

Figure 4.2. Number of mean BMD data points available by each of the 21 GBD world regions.

There were 130 eligible articles, with a total of 860 data points from 49 countries and 17 world regions. From Sanchez-Riera L et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission.

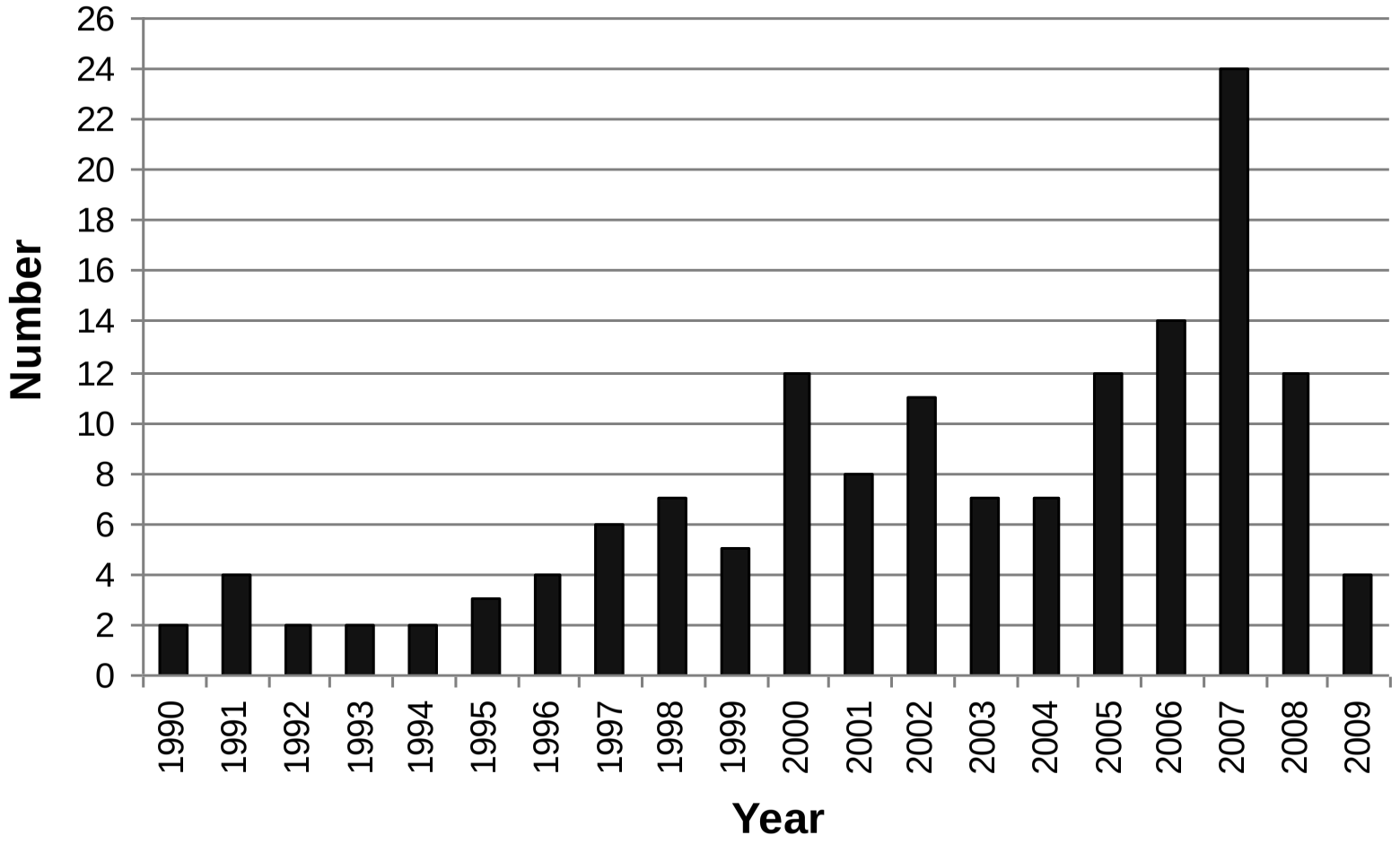

Figure 4.3. Number of publications from 1990 to 2010.

Table 4.1. Statistical differences between overall risk of bias groups.

Risk of Bias	P	95% Confidence Interval
For males and females (adjusted for 124 clusters)		
Moderate	0.237	-.006 - 0.022
High	0.360	-.035 - 0.013
For males (adjusted for 48 clusters)		
Moderate	0.827	-0.028 - 0.035
High	0.124	-0.053 - 0.006
For females (adjusted for 106 clusters)		
Moderate	0.532	-0.011 - 0.021
High	0.477	-0.037 - 0.017

P values are for comparing to studies with low risk of bias after adjustment by age. No significant difference was found for low risk of bias compared to moderate or high risk of bias groups in men, women or both sexes together.

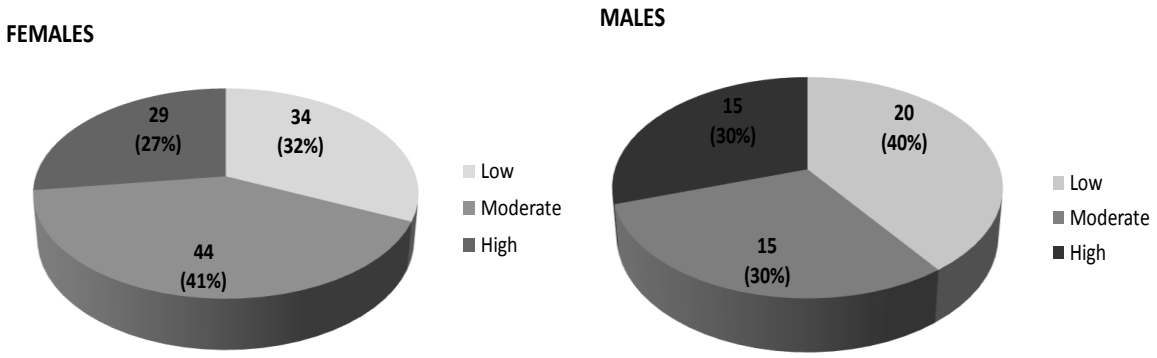

Figure 4.4. Distribution of studies in selection bias groups for females and males.

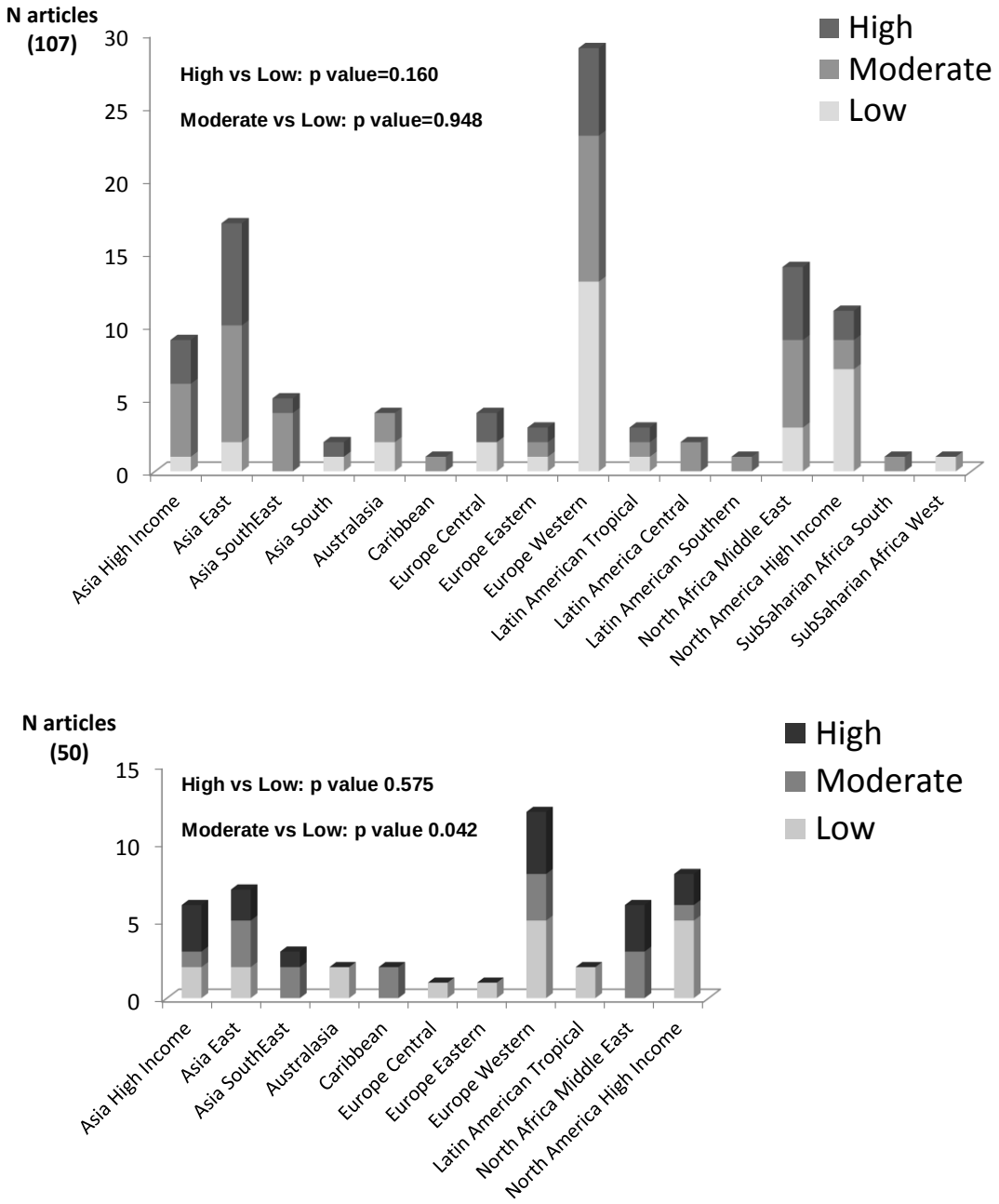

Figure 4.5. Selection bias-group distribution in females (upper) and males (lower)

Table 4.2. Final selection of studies from risk factor-disease relationship search strategy from the systematic review.

Citation	Abrahamsen B. et al 2006	Blaizot S. et al 2010	Kung, A. et al 2007	McLean, R R. et al 2008	Pinheiro, M. et al 2006
Country	Denmark	France	China, Hong Kong SAR	United States	Brazil
Outcome	Osteoporotic fracture	Non-vertebral fracture	Any fracture	Hip fracture	Osteoporotic fracture
Overall study sample size (collected)	872	781	1400	1002	275
Overall Level of Bias	Low risk of bias.	Low risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias
Follow-up period (months)	120	120	60	48	60
Anatomical location for the exposure measure	Femoral Neck	Femoral Neck	Femoral Neck	Femoral Neck	Femoral Neck
Parameter type for the effect size	Relative Risk	Hazard Ratio	Relative Risk	N/A	Hazard Ratio
Age Start	48	50	45	N/A	60
Age End	58	100	100	N/A	100
Mean age (SD) if given	-	-	63.4 (8.3)	75.3 (4.9)	75.2 (6.4)

Citation	Abrahamsen B. et al 2006	Blaizot S. et al 2010	Kung, A. et al 2007	McLean, R R. et al 2008	Pinheiro, M. et al 2006
Sex	Female	Male	Female	Both	Female
Parameter Value	1.32	1.27-1.42 (depending on skeletal site of measurement)	2	N/A	2.01
Lower CL	1.02	N/A	1.6	N/A	1.27
Upper CL	1.7	N/A	2.5	N/A	3.18
%CI	95% CI	95% CI	95% CI	N/A	95% CI
P value	0.01	<0.05	<0.01	N/A	0.003
Exposure unit for effect size (BMD value, T score SD, osteoporosis status, etc.)	Relative Risk per SD reduction in the T score	Relative Risk per SD reduction in BMD	1 SD reduction in the BMD value (g/cm^2)	N/A	1 SD reduction in the BMD value (g/cm^2)

References: (Abrahamsen, Vestergaard et al. 2006; Pinheiro, Castro et al. 2006; Kung, Lee et al. 2007; McLean, Jacques et al. 2008; Blaizot, Delmas et al. 2011). All prospective longitudinal studies. Pinheiro M et al was not population-based but it was well adjusted and coming from a region with not much data on RR BMD-fractures. N/A: non-applicable; SD: standard deviation; CI: confidence interval; BMD: bone mineral density.

4.2 Results for Risk Factor Levels of Exposure: Worldwide Distribution of Bone Mineral Density

Worldwide distributions of mean BMD for people aged 50 years and over for 1990 and 2010 are shown in Figure 4.6. Asia and Africa were the world regions with the lowest values of FNBMD, while High-Income North America, Caribbean and Eastern Europe showed the highest FNBMD values both for men and women. Although age-adjusted data showed an improving trend of the FNBMD values over time in preliminary analysis (Sanchez-Riera, Wilson et al. 2010), especially in Asia and Western Europe, FNBMD at a population level decreased in some regions due to the ageing of the population.

4.3 Low Bone Mineral Density Burden as a Fraction of Falls Burden

Population attributable fractions (PAFs) of FNBMD for falls were generally higher for females compared to males both for 1990 and 2010. In general, world regions with low GDP showed the highest PAFs (Asia East and South-East, Sub-Saharan Africa East and West), with the exception of Eastern Europe. However, big disparities in PAFs were observed among high income countries, even within the same world region; e.g., Scandinavian countries compared to UK (Figure 4.7).

In 1990 global DALYs and deaths attributable to low BMD constituted 12.1% and 29.6% of all falls-related DALYs and deaths, respectively. These percentages increased slightly to 14.8% and 34.7% for 2010 estimates (Table 4.3).

4.4 Health Burden due to Low Bone Mineral Density: DALYs, YLDs, YLLs and Deaths

Global deaths and DALYs attributable to low BMD increased from 103,000 and 3,125,000 in 1990 to 188,000 and 5,216,000 in 2010 respectively (Table 4.4). The percentage of low BMD in the total global burden almost doubled from 1990 (0.12%) to 2010 (0.21%), with both YLLs and YLDs increasing significantly in both sexes (Table 4.4). In population aged 50-69 years, such percentages increased to 0.41% for 1990 and 0.5% for 2010, and were even higher in population aged 70 years and above (0.64% and 0.79%, respectively) (http://www.healthdata.org/gbd). The fraction of the total regional burden increased in all regions except the Caribbean and Oceania. Asia East and South were the major contributing regions to the increase of the global burden of low BMD. Rates of global DALYs per 100,000 population increased remarkably from 1990 to 2010, but the increase was modest with age-standardization (Table 4.5), which reflects population growth and ageing. Rates were higher in Western Europe, Central Europe and High-Income Asia Pacific, while the highest age-standardized rates were more frequently found in developing regions like Sub-Saharan Africa East and West, Oceania, Asia East and South (Table 4.5 and Figure 4.8). For all time periods, YLLs contributed to the global burden of low BMD slightly more than YLDs, representing 51%, 54% and 53% of all DALYs for 1990, 2005 and 2010, respectively (Table 4.4).

When looking at sex groups, males obtained more DALYs than females for all analysed time periods, with a gap between both sexes that tended to progressively increase from 1990 to 2010, with 56%, 59% and 60% of all DALYs corresponding to

males for 1990, 2005 and 2010, respectively (Table 4.4). Differences between sexes were more remarkable for YLLs than for YLDs for all years. Rates of DALYs per 100,000 population for all ages increased from 1990 to 2010 in both sexes separately (66.06 vs 89.37 in males and 51.73 vs 61.82 in females). Rates increased dramatically within the age group 50-69 years compared with all ages estimates, again more remarkably in men (315.85 and 329.78 for 1990 and 2010 respectively) than in women (192.34 and 177.84 for 1990 and 2010 respectively). Rates of DALYs became around three-fold in ages from 70 years onwards from those in the 50-69 age group, also showing considerably greater values in males than females for both 1990 (861.81 vs 568.97) and 2010 (924.21 vs 569.43). Deaths (mean followed by uncertainty interval 95%) attributable to low BMD almost doubled in males from 1990 to 2010, from 52,816 (43,882-69,605) to 103,440 (67,743-124,596), while in females they increased around 60% between both time periods, with 50,455 (40,408-62,110) and 84,146 (57,863-102,441) deaths in 1990 and 2010, respectively (http://www.healthdata.org/gbd).

For all diseases, injuries and risk factors, data on DALYs, YLDs, YLLs and deaths can be visualised online by region, country, year, age and sex (http://www.healthdata.org/gbd).

4.5 Health Burden due to Low Bone Mineral Density Compared to Other Risk Factors in the GBD 2010 study

Low BMD ranked low in terms of attributable DALYs compared to most risk factors, such as dietary factors, high blood pressure, smoking, alcohol use, high fasting plasma glucose, high body mass index, high cholesterol and low physical activity (Figure 4.9) (Lim, Vos et al. 2012).

When dietary risk factors and occupational risk factors were clustered into one category each, low BMD ranked 23rd among 25 risk factor categories globally for 2010 for all ages together (20th among 21 clusters for 1990) (Figure 4.9). By region, the highest ranks for low BMD were observed in Western Europe and High Income Asia Pacific, ranked 12th and 13th respectively, followed by Central Europe, Australasia, and High Income North America at 15th, and Asia East at 16th (Figure 4.9). Improvement of the ranking for all regions and both sexes was observed in older ages in comparison to the general population (Figure 4.10 and Figure 4.11) When ranking was looked for population 70 years and over only, low BMD moved to 13th position globally over 21 clusters of risk factors for the same time period. (11th out of 17 clusters for 1990) (Figure 4.11). Great shifts in the rankings of YLDs and YLLs separately were similarly observed with the selection of elderly population, as shown in Figure 4.12 to Figure 4.17, with low BMD becoming part of the 10 top risk factors for YLDs in the age group ≥ 70 years (Figure 4.14). Results were similar for females and males, with changes of one position maximum in the rank within the sex group (http://www.healthdata.org/gbd).

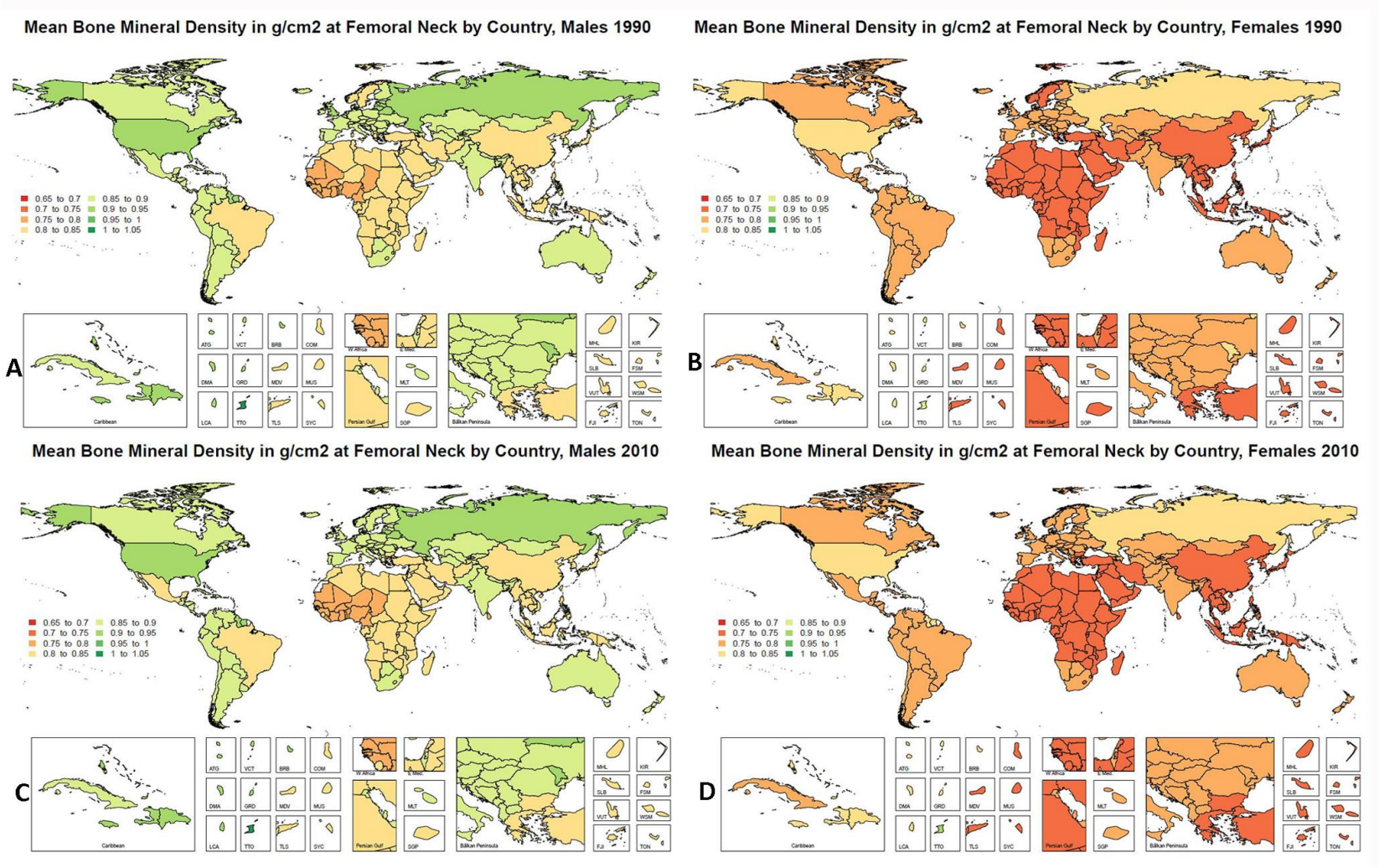

Figure 4.6. Word distribution of standardised bone mineral density in g/cm2 at the femoral neck at country level.

(A) Men, 1990; (B) women, 1990; (C) men, 2010; (D) women, 2010. From Sanchez-Riera et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission by author's copyright.

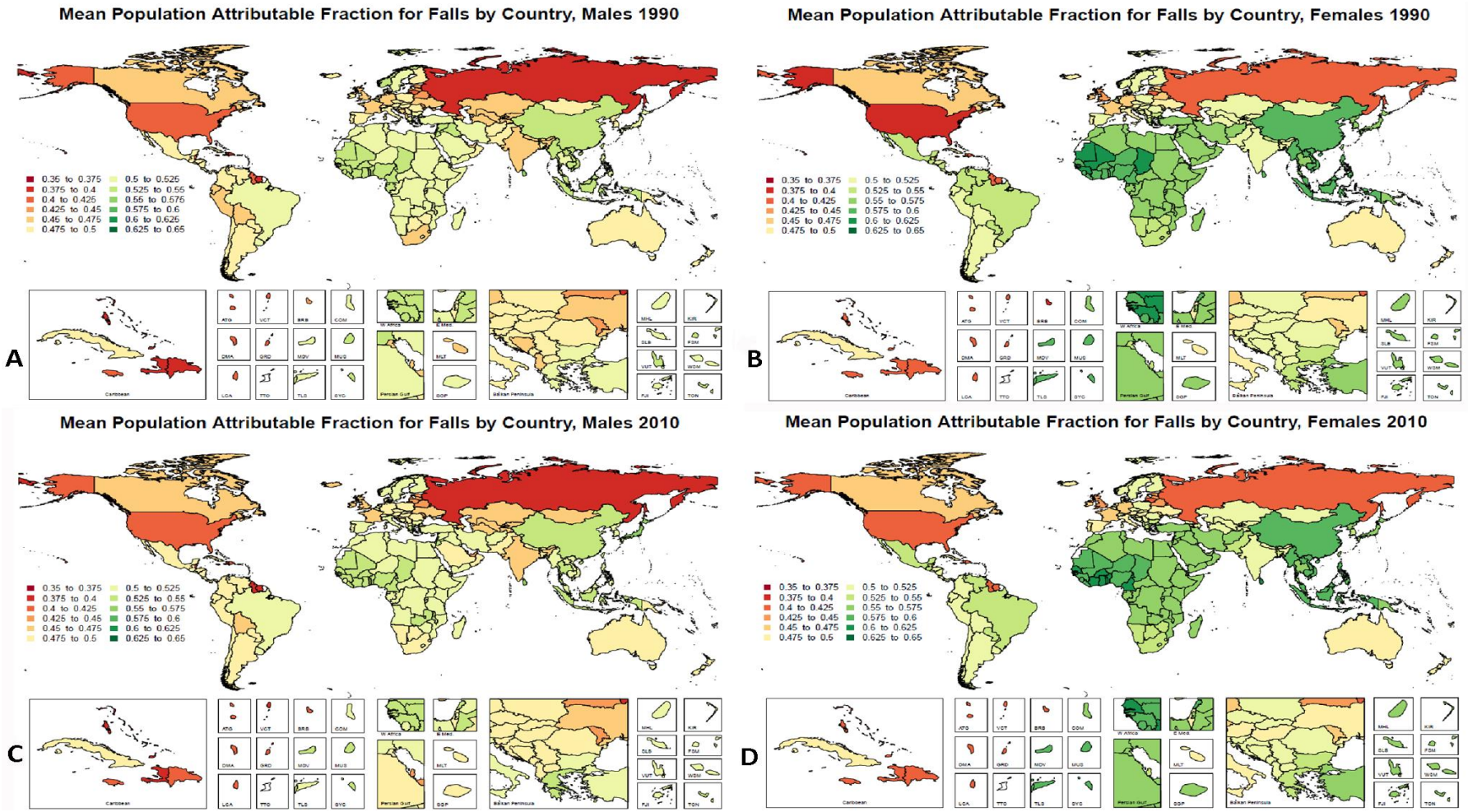

Figure 4.7. Age-standardized population attributable fraction (PAF) of low bone mineral density for falls.

Values are expressed on 0–1 scale. (A) Men, 1990; (B) women, 1990; (C) men, 1990; (D) women, 2010. Age standardization was obtained using the global standard proposed by the WHO in 2001 (http://www.who.int/healthinfo/paper31.pdf). From Sanchez-Riera L et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission by author's copyright.

Table 4.3. Burden of low bone mineral density as a percentage of falls-related burden by GBD region and year

	1990				2010			
Region	**DALYs**	**YLLs**	**YLDs**	**Deaths**	**DALYs**	**YLLs**	**YLDs**	**Deaths**
Asia Pacific, High Income	16.3 (13.6 - 19.3)	21.7 (18.8 - 25.8)	14.4 (11.4 - 17.6)	38.0 (33.3 - 42.9)	22.3 (18.8 - 25.8)	38.2 (32.1 - 42.6)	18.1 (14.7 - 21.5)	50.5 (44.3 - 55.6)
Asia, Central	8.0 (6.4 - 9.4)	4.9 (4.1 - 5.6)	9.7 (7.4 - 11.9)	12.7 (10.9 - 14.3)	8.5 (6.9 - 10.1)	6.0 (4.7 - 7.3)	9.7 (7.6 - 11.7)	14.0 (11.6 - 16.3)
Asia, East	13.7 (11.6 - 15.6)	14.6 (11.5 - 16.9)	12.7 (10.4 - 15.0)	32.8 (27.8 - 36.7)	17.5 (15.2 - 20.0)	21.8 (18.6 - 25.7)	14.1 (11.7 - 16.7)	39.7 (35.4 - 44.6)
Asia, South	8.9 (7.0 - 11.0)	9.1 (7.0 - 11.5)	8.7 (6.2 - 11.1)	21.6 (17.5 - 25.8)	11.9 (9.0 - 14.8)	13.7 (10.1 - 17.8)	9.2 (6.7 - 11.7)	28.3 (21.8 - 34.4)
Asia, Southeast	13.8 (11.6 - 16.2)	17.7 (14.0 - 21.6)	10.5 (8.7 - 12.4)	35.3 (30.3 - 40.8)	16.3 (13.6 - 19.1)	23.2 (19.3 - 26.8)	11.3 (9.3 - 13.3)	40.1 (35.1 - 44.9)
Australasia	15.0 (11.1 - 18.7)	27.2 (21.6 - 32.3)	12.7 (9.1 - 16.4)	40.5 (30.5 - 48.2)	17.3 (12.9 - 21.5)	35.2 (27.3 - 41.6)	14.3 (10.3 - 18.2)	44.3 (32.6 - 52.7)
Caribbean	13.6 (10.7 - 16.3)	19.0 (14.7 - 22.9)	9.4 (7.3 - 11.6)	36.8 (28.2 - 43.7)	12.6 (9.7 - 15.3)	24.8 (19.3 - 29.7)	8.3 (6.3 - 10.4)	40.3 (29.5 - 48.4)
Europe, Central	18.9 (16.0 - 21.8)	26.4 (23.2 - 29.4)	14.6 (12.0 - 17.5)	39.9 (34.2 - 44.7)	20.0 (16.9 - 23.2)	32.0 (28.1 - 35.2)	16.0 (13.2 - 19.0)	43.1 (37.1 - 47.8)
Europe, Eastern	11.1 (7.7 - 14.4)	13.8 (9.6 - 17.3)	9.7 (6.4 - 13.0)	24.0 (16.9 - 29.9)	12.7 (8.7 - 16.0)	16.1 (11.0 - 20.2)	10.3 (6.7 - 13.6)	25.9 (17.9 - 32.3)
Europe, Western	18.5 (15.8 - 21.3)	30.9 (27.0 - 34.8)	14.4 (12.1 - 16.6)	40.9 (34.6 - 46.7)	20.1 (17.0 - 23.1)	36.8 (32.5 - 40.6)	16.1 (13.4 - 19.1)	43.7 (37.1 - 48.9)
Latin America, Andean	9.3 (7.4 - 11.2)	9.6 (7.6 - 11.6)	9.1 (6.9 - 11.5)	23.4 (19.2 - 27.3)	11.7 (9.2 - 13.9)	13.4 (10.9 - 15.8)	10.8 (8.0 - 13.5)	30.2 (24.8 - 34.6)
Latin America, Central	11.0 (9.5 - 12.5)	11.4 (10.0 - 13.1)	10.5 (8.4 - 12.6)	27.5 (24.4 - 30.7)	14.7 (12.5 - 16.9)	18.7 (15.5 - 21.2)	11.5 (9.4 - 13.6)	36.1 (31.5 - 40.1)
Latin America, Southern	14.3 (10.9 - 17.5)	20.1 (16.2 - 23.8)	12.1 (8.6 - 15.6)	37.3 (29.8 - 43.1)	15.3 (12.0 - 18.7)	26.2 (21.1 - 30.8)	12.8 (9.8 - 16.0)	42.0 (33.1 - 49.0)
Latin America, Tropical	11.3 (9.1 - 13.6)	11.2 (9.0 - 14.0)	11.4 (8.8 - 14.2)	26.8 (21.8 - 32.1)	17.1 (12.9 - 20.8)	22.6 (15.8 - 27.2)	13.6 (10.3 - 16.8)	40.0 (31.7 - 46.9)

	1990				2010			
Region	**DALYs**	**YLLs**	**YLDs**	**Deaths**	**DALYs**	**YLLs**	**YLDs**	**Deaths**
North Africa / Middle East	8.6 (7.3 - 10.0)	5.6 (4.2 - 7.0)	10.5 (8.8 - 12.2)	17.1 (13.6 - 20.7)	10.5 (9.1 - 11.9)	8.9 (7.8 - 10.3)	11.2 (9.4 - 13.1)	23.2 (20.8 - 26.0)
North America, High Income	13.5 (9.4 - 17.4)	24.1 (17.3 - 30.2)	8.7 (5.7 - 11.6)	34.9 (23.1 - 43.7)	17.2 (11.4 - 22.7)	31.3 (21.8 - 39.1)	10.5 (7.0 - 13.8)	38.0 (25.0 - 47.1)
Oceania	10.2 (8.1 - 12.5)	9.2 (6.4 - 12.4)	10.8 (8.4 - 13.4)	20.9 (16.1 - 26.2)	10.7 (8.3 - 13.0)	11.6 (7.8 - 15.7)	10.0 (7.7 - 12.1)	24.5 (18.1 - 30.5)
Sub-Saharan Africa, Central	6.9 (4.0 - 12.0)	6.0 (2.6 - 14.3)	9.5 (7.4 - 11.7)	16.2 (8.7 - 30.7)	7.1 (4.6 - 11.0)	6.3 (3.1 - 13.0)	9.3 (7.3 - 11.4)	16.7 (9.9 - 28.7)
Sub-Saharan Africa, East	9.4 (6.2 - 13.1)	9.6 (5.4 - 15.0)	9.4 (7.8 - 11.0)	24.2 (15.9 - 32.0)	12.0 (9.0 - 14.4)	13.1 (8.8 - 16.2)	9.6 (8.0 - 11.4)	29.7 (22.8 - 33.9)
Sub-Saharan Africa, Southern	9.6 (7.2 - 11.8)	14.7 (11.3 - 18.2)	8.0 (5.9 - 10.2)	31.0 (24.5 - 37.1)	10.7 (8.4 - 13.1)	17.6 (13.8 - 21.7)	8.8 (6.5 - 11.0)	34.9 (28.0 - 41.3)
Sub-Saharan Africa, West	5.1 (3.3 - 9.1)	4.1 (2.6 - 8.7)	10.9 (8.9 - 13.0)	13.9 (9.8 - 23.1)	6.7 (5.1 - 9.0)	5.7 (4.1 - 8.4)	10.8 (9.0 - 12.6)	18.3 (14.0 - 23.7)
Global	**12.1 (11.1 - 13.2)**	**12.7 (11.3 - 14.7)**	**11.5 (10.3 - 12.8)**	**29.6 (27.4 - 32.0)**	**14.8 (13.4 - 16.0)**	**17.3 (15.4 - 19.1)**	**12.7 (11.4 - 13.9)**	**34.7 (32.2 - 37.1)**

Values with 95% uncertainty interval represent low bone mineral density burden expressed as percentage (%) of falls-related burden. All ages, both sexes. DALYs: disability-adjusted life years; YLL: years of life lost due to premature mortality; YLDs: years lived with disability; GBD: global burden of diseases. From Sanchez-Riera L et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission by author's copyright.

Table 4.4. Global burden of low bone mineral density: Deaths, DALYs, YLLs and YLDs

		Deaths		DALYs		YLLs		YLDs	
Year	Sex	Absolute	Percent	DALYs	Percent	Absolute	Percent	Absolute	Percent
1990	Both	103,270	0.22	3,125,166	0.12	1,595,178	0.08	1,529,989	0.26
		(90,672 - 124,230)	(0.20 - 0.27)	(2,588,901 - 3,811,443)	(0.10 - 0.15)	(1,411,360 - 1,944,972)	(0.07 - 0.10)	(1,044,409 - 2,121,696)	(0.19 - 0.34)
1990	Female	50,455	0.23	1,361,202	0.12	669,752	0.08	691,450	0.23
		(40,408 - 62,110)	(0.19 - 0.29)	(1,101,627 - 1,685,725)	(0.10 - 0.14)	(543,744 - 809,200)	(0.07 - 0.10)	(468,513 - 989,670)	(0.16 - 0.31)
1990	Male	52,816	0.21	1,763,964	0.13	925,426	0.09	838,539	0.30
		(43,822 - 69,605)	(0.18 - 0.28)	(1,448,305 - 2,207,969)	(0.11 - 0.16)	(771,153 - 1,221,801)	(0.07 - 0.12)	(569,103 - 1,184,753)	(0.22 - 0.39)
2005	Both	168,049	0.33	4,642,366	0.18	2,526,614	0.14	2,115,752	0.29
		(125,643 - 194,351)	(0.24 - 0.37)	(3,674,161 - 5,641,433)	(0.15 - 0.22)	(1,859,581 - 2,932,549)	(0.10 - 0.16)	(1,446,478 - 2,971,623)	(0.21 - 0.38)
2005	Female	76,471	0.33	1,923,418	0.17	978,753	0.13	944,665	0.25
		(51,059 - 91,865)	(0.22 - 0.39)	(1,465,495 - 2,382,540)	(0.13 - 0.21)	(648,292 - 1,172,601)	(0.09 - 0.15)	(637,877 - 1,337,991)	(0.18 - 0.33)
2005	Male	91,578	0.32	2,718,948	0.20	1,547,861	0.15	1,171,086	0.33
		(59,947 - 108,685)	(0.21 - 0.39)	(2,020,242 - 3,341,576)	(0.15 - 0.24)	(1,016,485 - 1,848,546)	(0.10 - 0.18)	(794,783 - 1,671,341)	(0.24 - 0.44)
2010	Both	187,586	0.36	5,216,399	0.21	2,753,010	0.16	2,463,388	0.32
		(140,636 - 219,906)	(0.27 - 0.42)	(4,132,978 - 6,418,307)	(0.17 - 0.25)	(2,031,594 - 3,242,599)	(0.12 - 0.19)	(1,699,328 - 3,490,237)	(0.23 - 0.41)
2010	Female	84,146	0.35	2,111,329	0.19	1,045,989	0.15	1,065,340	0.26
		(57,863 - 102,441)	(0.25 - 0.43)	(1,627,353 - 2,618,461)	(0.15 - 0.23)	(725,341 - 1,267,368)	(0.10 - 0.18)	(719,873 - 1,496,345)	(0.19 - 0.35)
2010	Male	103,440	0.36	3,105,070	0.23	1,707,021	0.17	1,398,048	0.37
		(67,743 - 124,596)	(0.24 - 0.43)	(2,295,173 - 3,830,642)	(0.17 - 0.28)	(1,089,516 - 2,077,040)	(0.11 - 0.21)	(961,318 - 1,998,927)	(0.27 - 0.49)

Values with 95% uncertainty interval are expressed in absolute values and percentage of all GBD causes.

DALYs: disability-adjusted life years; YLL: years of life lost due to premature mortality; YLDs: years lived with disability. From Sanchez-Riera L et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission by author's copyright.

Table 4.5. Rates of DALYs per 100,000 population by GBD region in 1990 and 2010

	1990				2010			
Location	**All Ages**		**Age-Standardized**		**All Ages**		**Age-Standardized**	
Asia Pacific, High-income	80.79	(59.46-106.37)	65.85	(48.44-86.62)	138.31	(102.67-181.06)	63.43	(47.48-82.93)
Asia, Central	38.02	(26.64-50.90)	54.17	(37.79-72.72)	37.46	(26.80-52.41)	49.41	(35.15-69.01)
Asia, East	68.64	(56.02-84.10)	94.54	(77.36-116.21)	92.00	(72.58-113.50)	86.45	(68.28-106.73)
Asia, South	44.15	(32.85-59.10)	86.92	(65.52-115.84)	64.87	(42.01-88.54)	102.87	(66.89-140.05)
Asia, Southeast	45.39	(35.50-55.66)	85.71	(66.39-104.44)	62.48	(46.36-77.96)	84.81	(62.64-105.55)
Australasia	87.20	(60.27-124.09)	69.28	(48.18-98.00)	117.27	(79.24-164.28)	67.52	(44.60-94.86)
Caribbean	48.02	(35.73-60.13)	66.22	(49.20-83.01)	62.56	(46.94-79.73)	66.16	(49.74-84.60)
Europe, Central	154.51	(121.21-192.20)	121.69	(95.48-151.15)	187.81	(141.40-245.17)	108.44	(82.07-142.07)
Europe, Eastern	60.65	(39.77-86.20)	45.32	(29.78-64.35)	85.59	(54.13-118.30)	54.61	(34.90-75.23)
Europe, Western	140.64	(108.32-181.16)	83.04	(63.72-107.39)	183.26	(140.75-239.56)	85.86	(65.50-112.71)
Latin America, Andean	35.06	(25.74-45.51)	67.45	(49.50-87.44)	36.57	(27.09-48.39)	50.41	(37.37-66.73)
Latin America, Central	27.00	(21.75-33.29)	51.84	(41.80-63.95)	35.65	(28.15-43.87)	47.45	(37.43-58.41)
Latin America, Southern	63.37	(44.87-86.13)	64.96	(45.86-88.32)	63.86	(45.05-87.23)	50.92	(35.90-69.74)

Location	1990				2010			
	All Ages		Age-Standardized		All Ages		Age-Standardized	
Latin America, Tropical	29.45	(21.24-39.82)	52.47	(37.74-70.95)	56.82	(37.06-75.07)	63.95	(41.54-84.41)
North Africa / Middle East	30.78	(23.18-40.86)	66.54	(50.20-88.00)	37.45	(27.85-49.71)	60.63	(45.36-80.72)
North America, High-income	43.48	(28.23-59.15)	31.57	(20.62-42.99)	70.82	(43.07-99.00)	41.83	(25.21-58.36)
Oceania	56.02	(39.92-76.49)	147.40	(106.54-199.03)	41.21	(30.75-55.27)	91.17	(69.18-118.80)
Sub-Saharan Africa, Central	30.92	(23.39-39.60)	77.97	(59.17-99.77)	27.08	(20.45-35.20)	73.34	(55.58-95.12)
Sub-Saharan Africa, Eastern	37.20	(29.19-48.64)	96.50	(75.27-125.60)	42.24	(28.34-53.42)	103.90	(69.87-131.93)
Sub-Saharan Africa, Southern	15.51	(10.70-21.08)	36.91	(25.43-50.07)	22.20	(15.40-30.10)	38.17	(26.33-51.75)
Sub-Saharan Africa, Western	46.15	(37.28-56.03)	114.76	(92.56-138.91)	44.07	(36.03-52.63)	108.31	(87.83-130.19)
Global	**58.95**	**(48.83-71.89)**	**77.89**	**(64.51-94.96)**	**75.71**	**(59.99-93.15)**	**79.87**	**(63.28-98.22)**

Values with 95% uncertainty intervals are rates of DALYs per 100.000 population. All ages, both sexes. Age-standardization was obtained using global standard proposed by the World Health Organization in 2001 (http://www.who.int/healthinfo/paper31.pdf). DALYs: disability-adjusted life years; GBD: global burden of diseases. From Sanchez-Riera L et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission by authors's copyright.

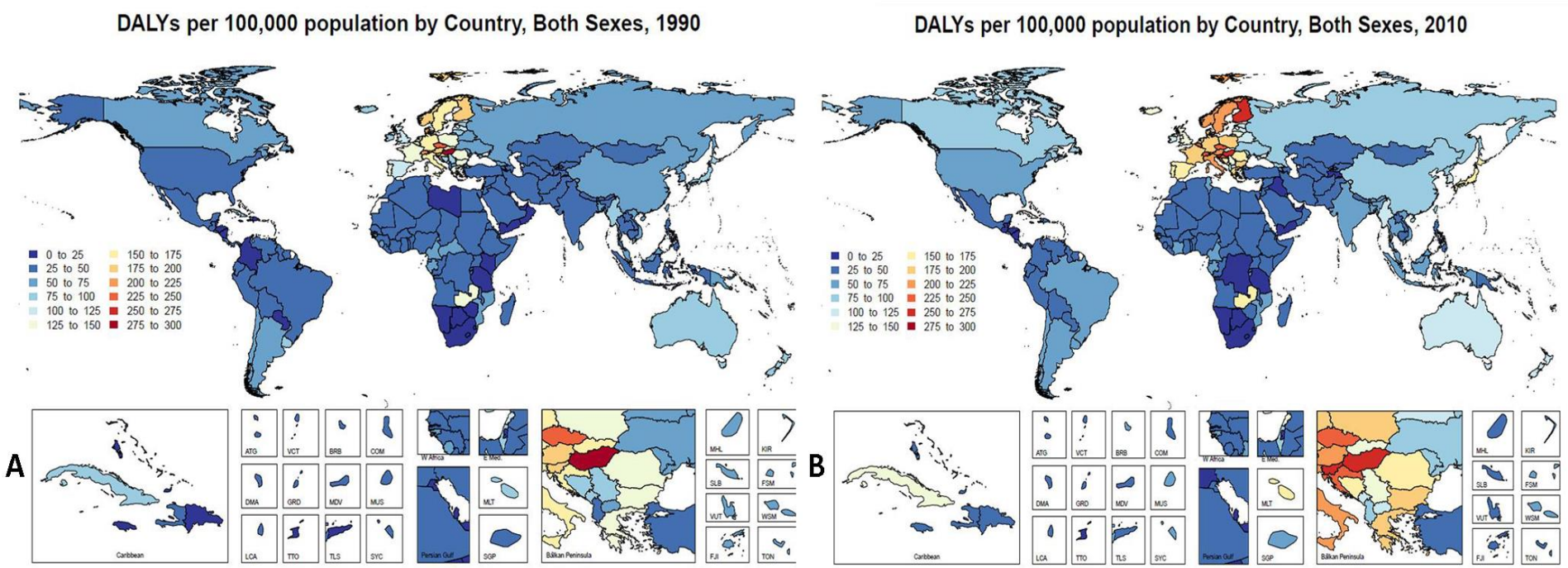

Figure 4.8. World distribution of disability-adjusted life years (DALYs) for low bone mineral density per 100 000 population at country level.

All ages, both sexes. (A) Estimations for 1990; (B) estimations for 2010 (for all estimations for 1990, 2005 and 2010 for men and women at country, region and super-region levels, please visit http://www.healthdata.org/gbd). From Sanchez-Riera L et al 2014 (Sanchez-Riera L, Carnahan E et al. 2014), with permission by author's copyright.

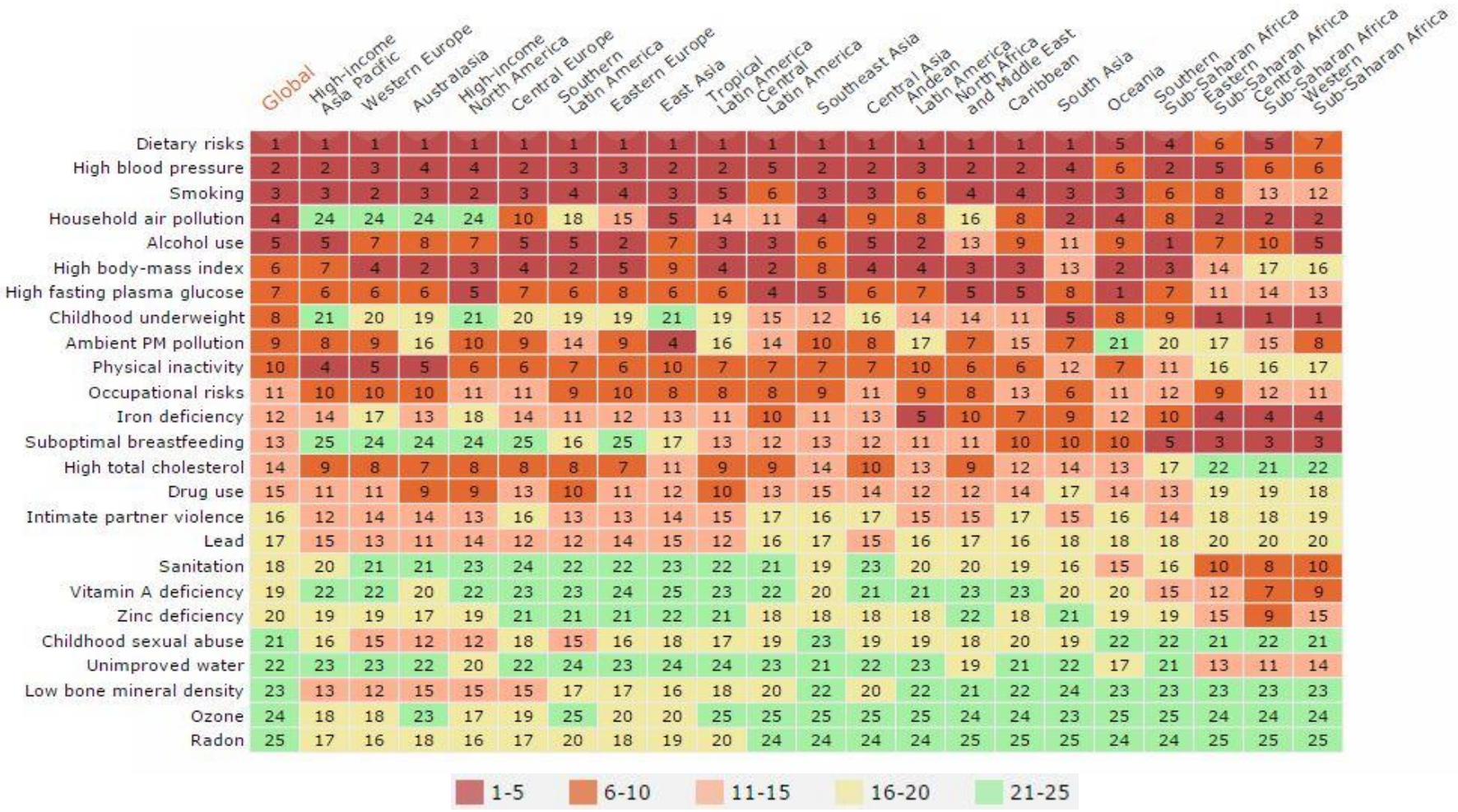

Figure 4.9. Ranking of Disability-Adjusted Life Years (DALYs) for all risk factors (all ages, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction (www.healthdata.org/gbd)

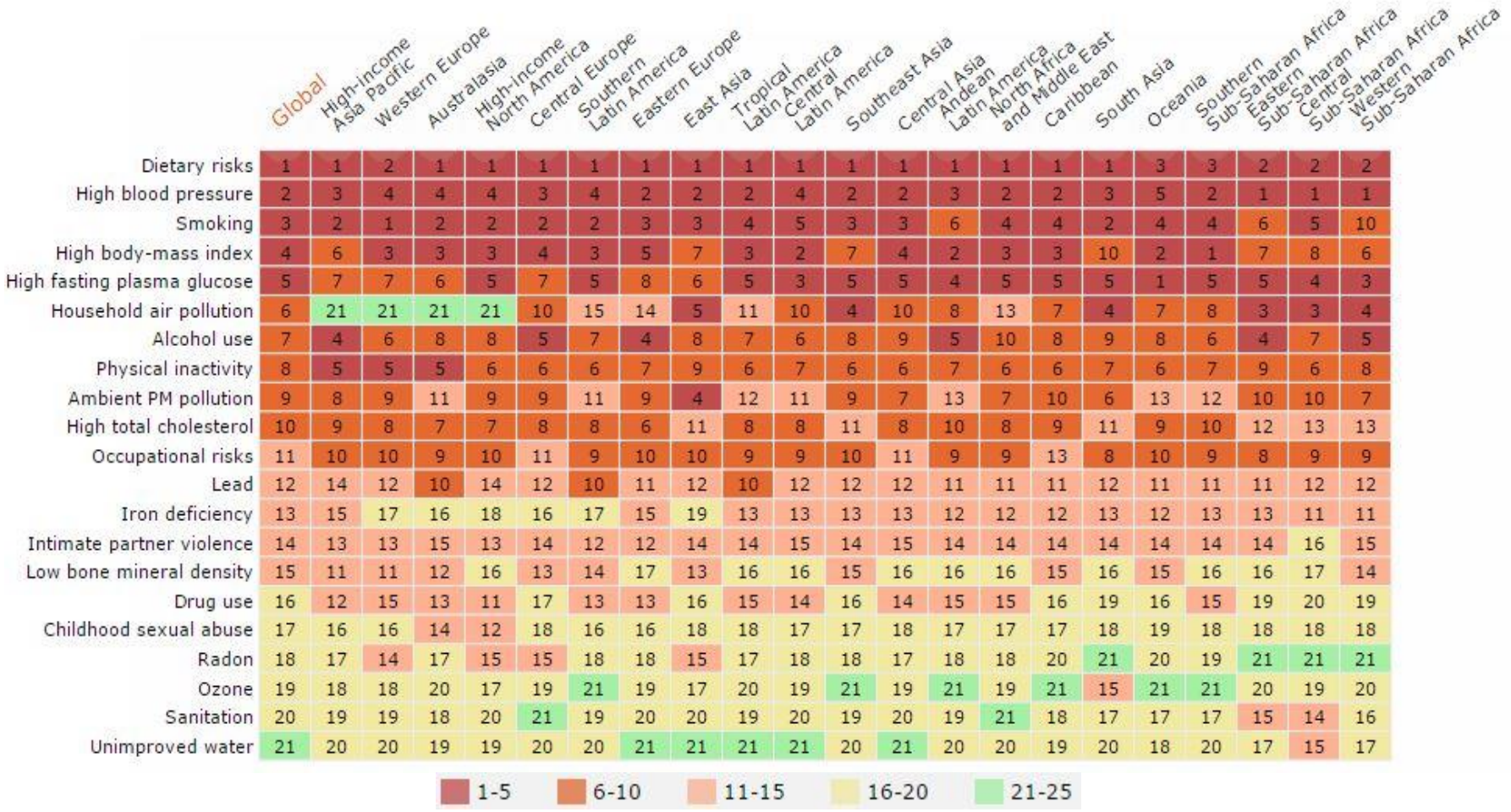

Figure 4.10. Ranking of Disability-Adjusted Life Years (DALYs) for all risk factors (ages 50-69, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

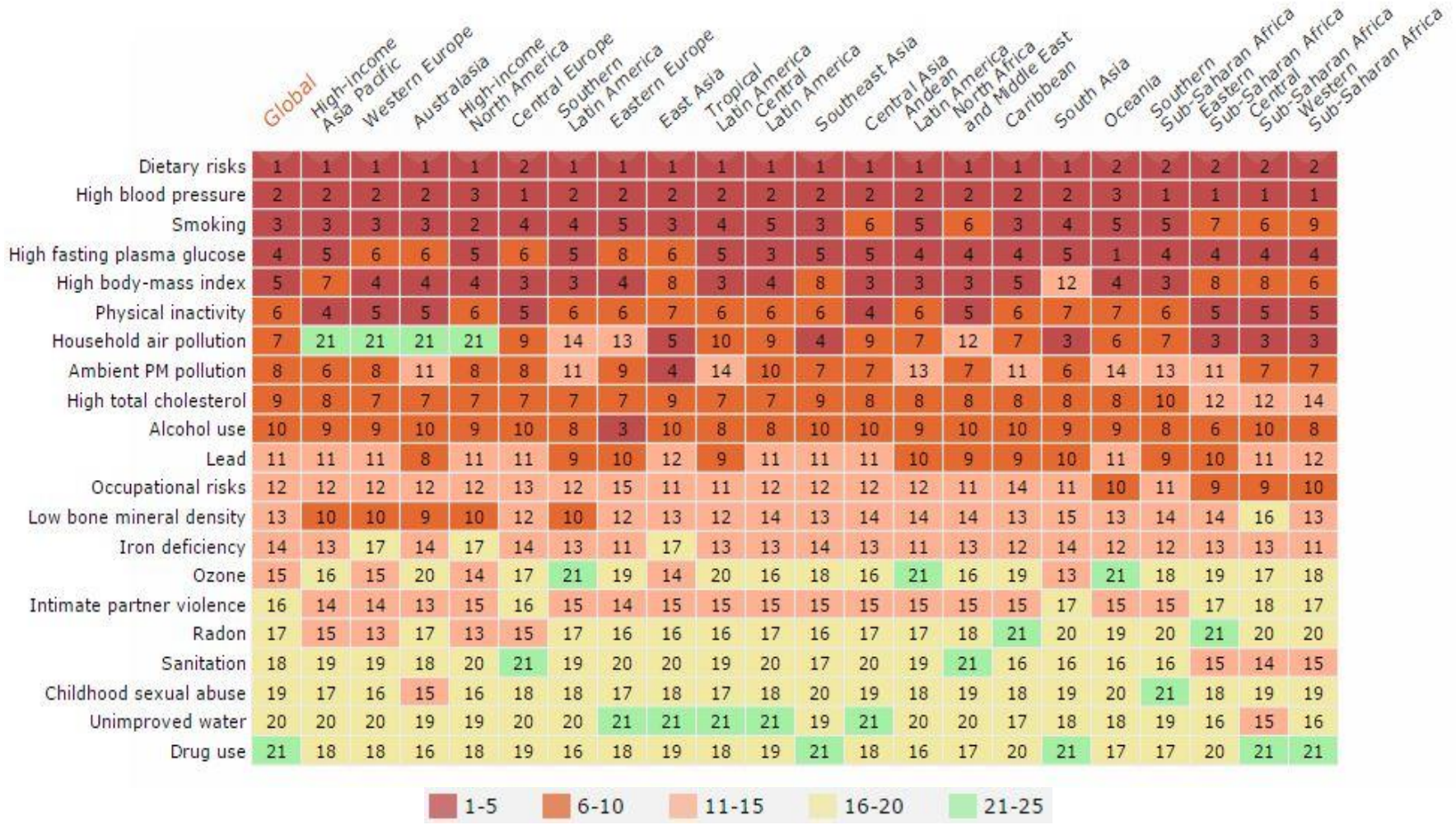

Figure 4.11. Ranking of Disability-Adjusted Life Years (DALYs) for all risk factors (ages ≥ 70, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

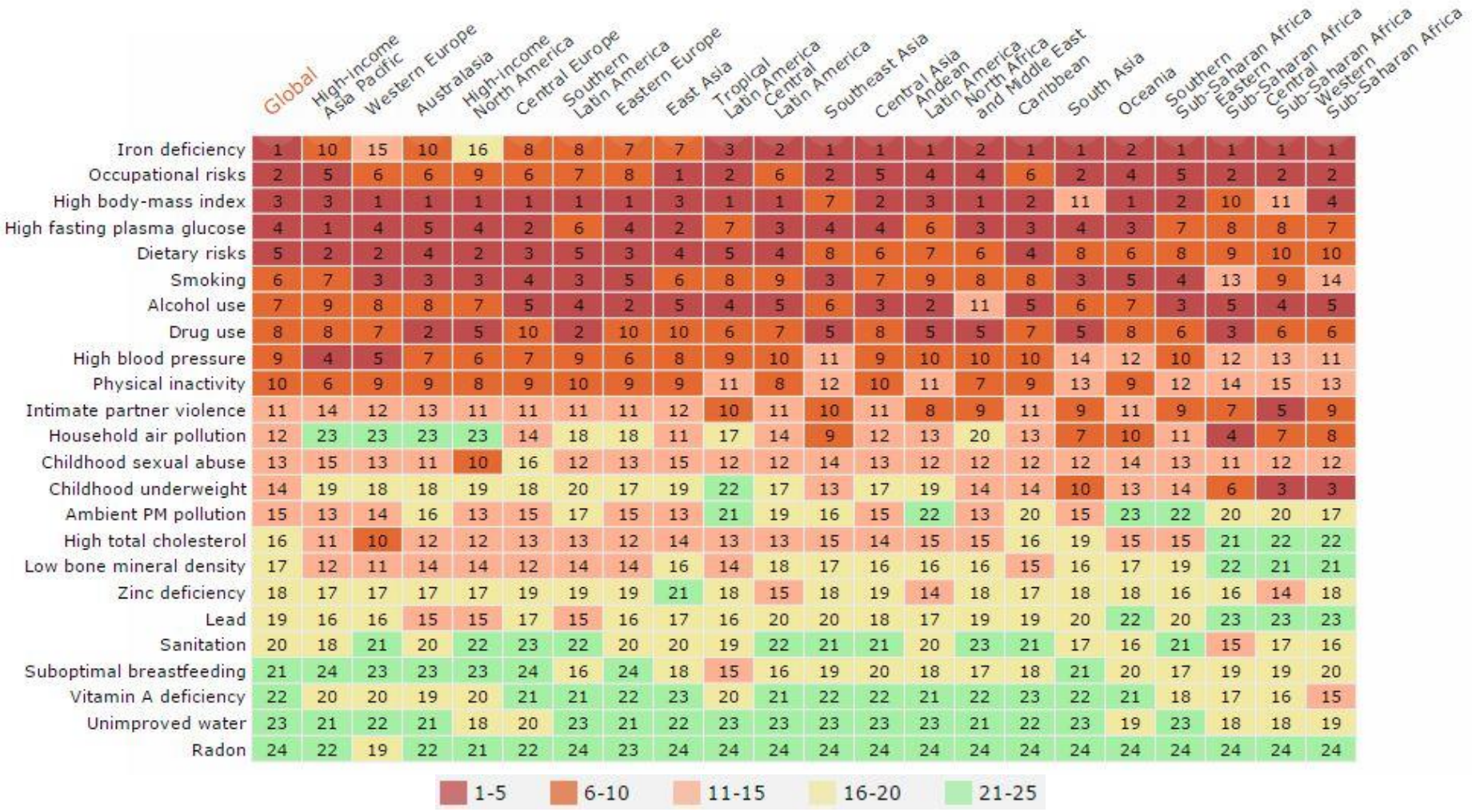

Figure 4.12. Ranking of Years Lived with Disability (YLDs) for all risk factors (all ages, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

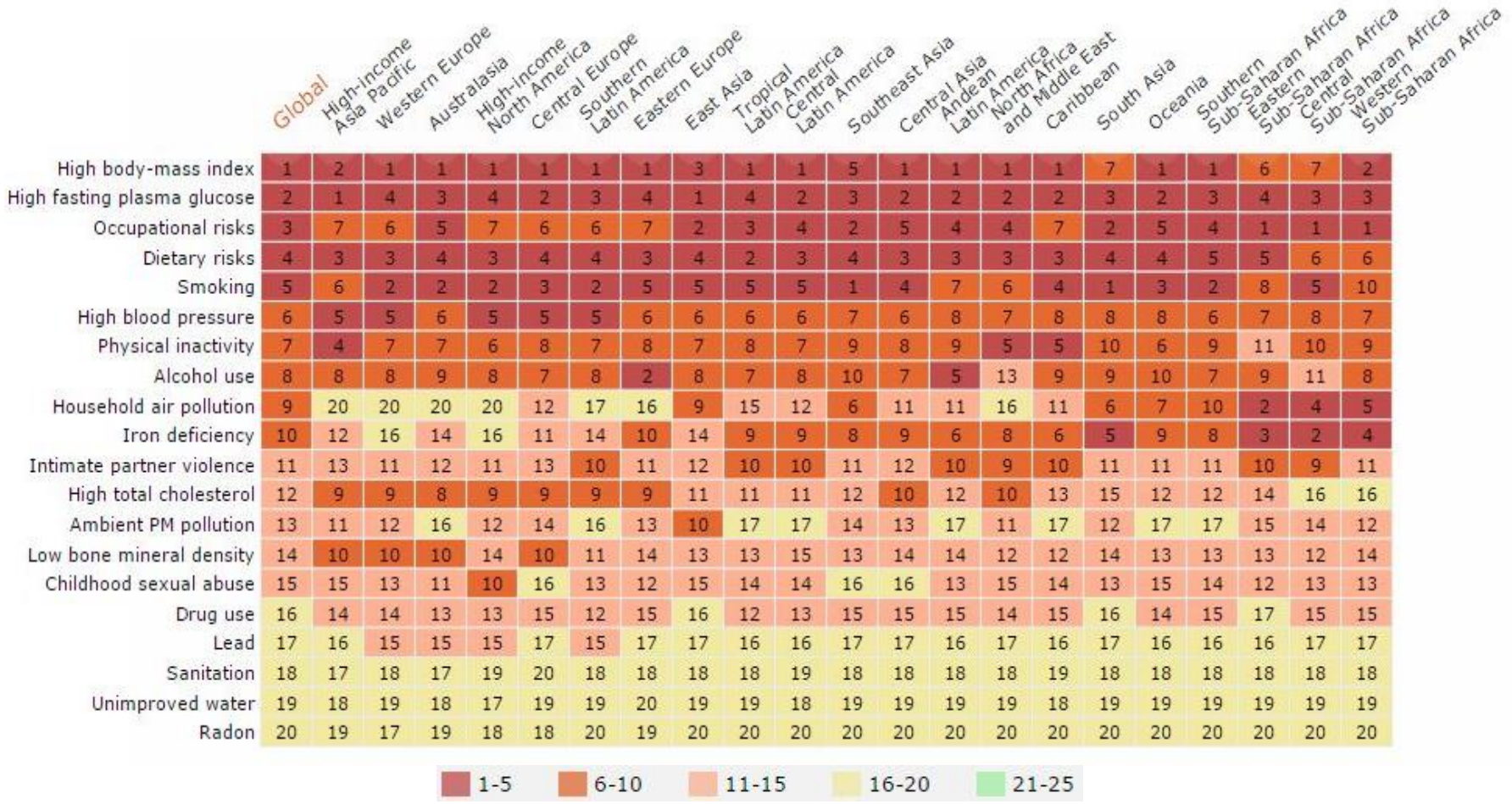

Figure 4.13. Ranking of Years Lived with Disability (YLDs) for all risk factors (ages 50-69, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

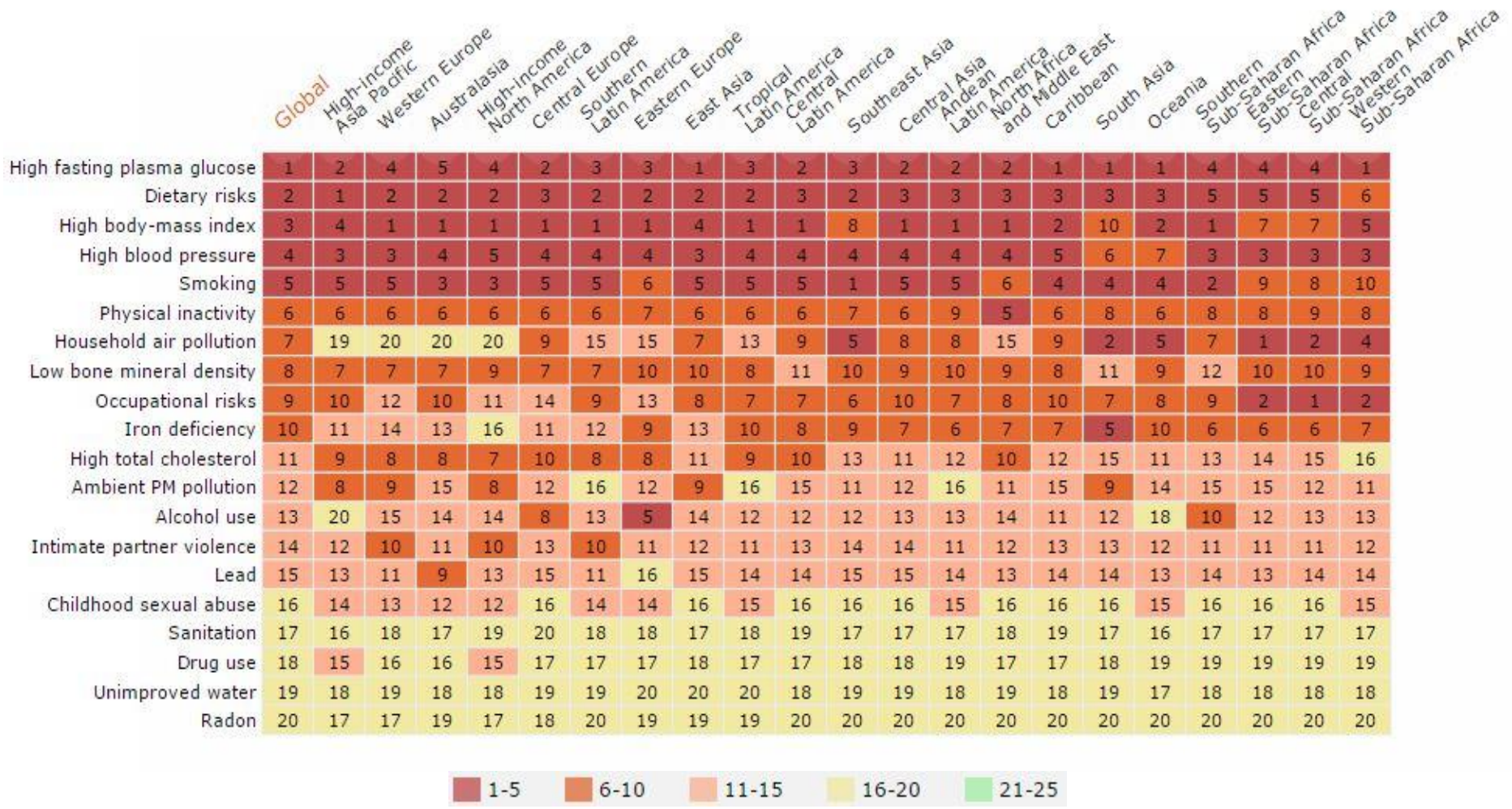

Figure 4.14. Ranking of Years Lived with Disability (YLDs) for all risk factors (ages ≥ 70, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction (www.healthdata.org/gbd)

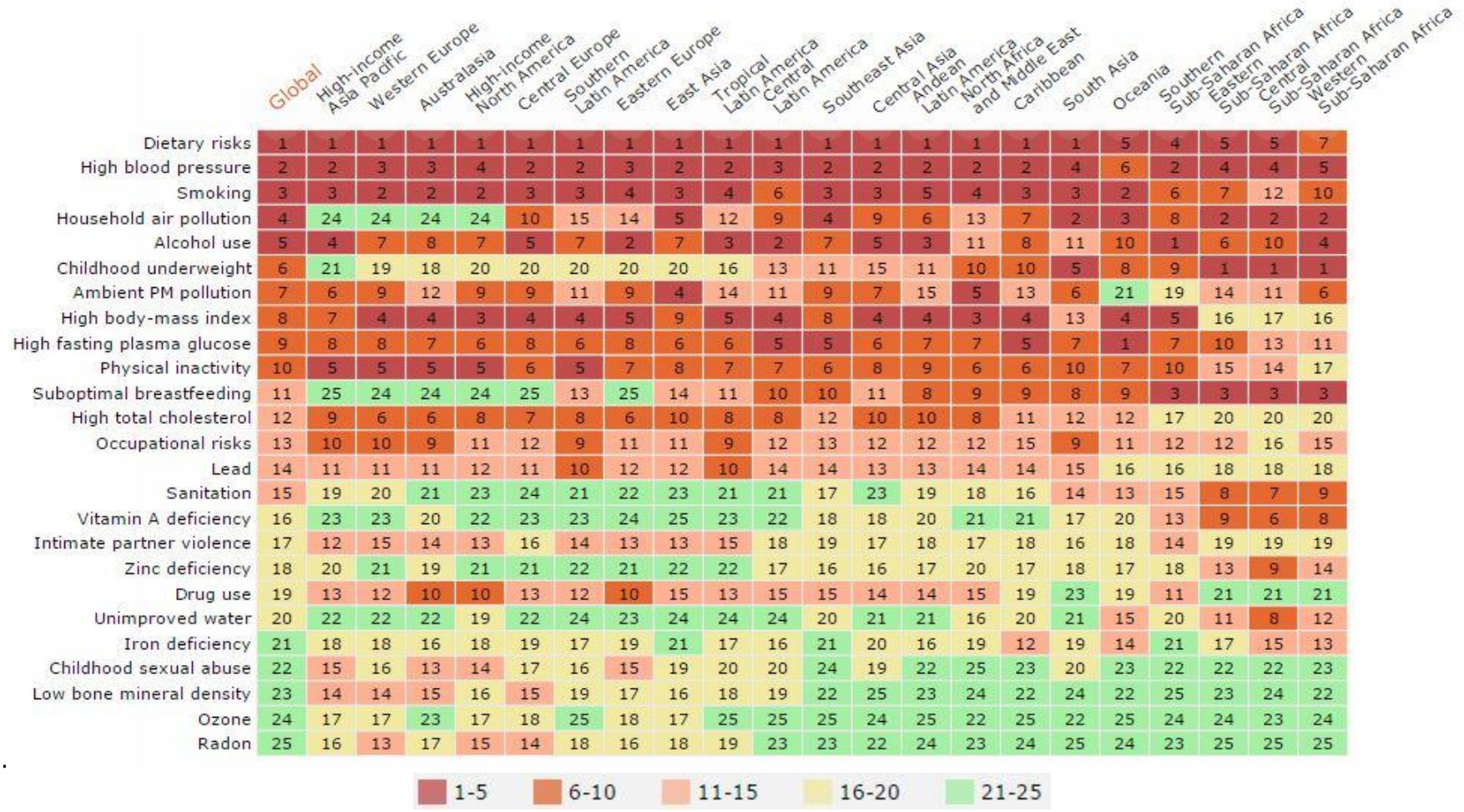

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Figure 4.15. Ranking of Years of Life Lost due to premature mortality (YLLs) for all risk factors (all ages, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

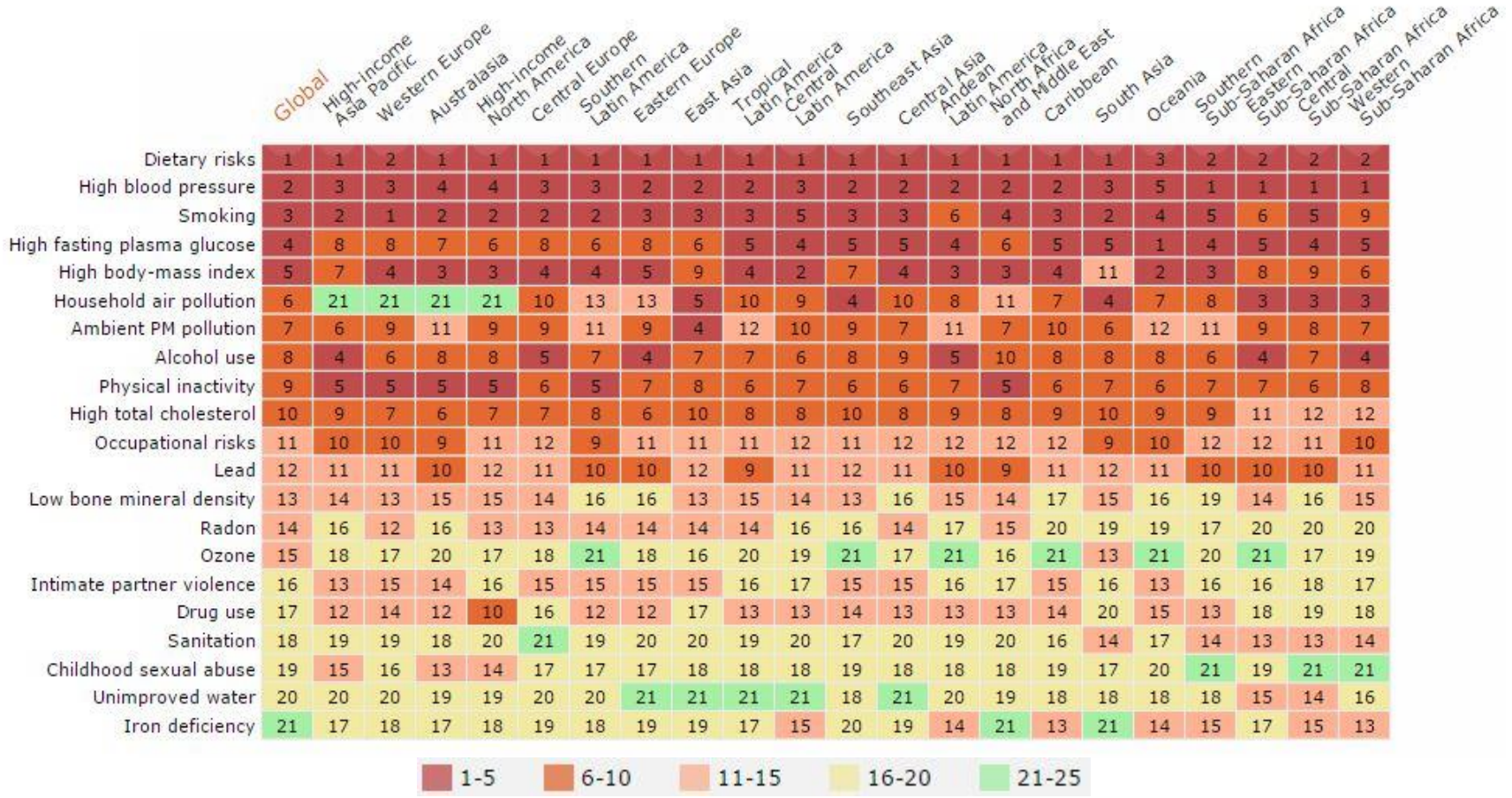

Figure 4.16. Ranking of Years of Life Lost due to premature mortality (YLLs) for all risk factors (ages 50-69, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

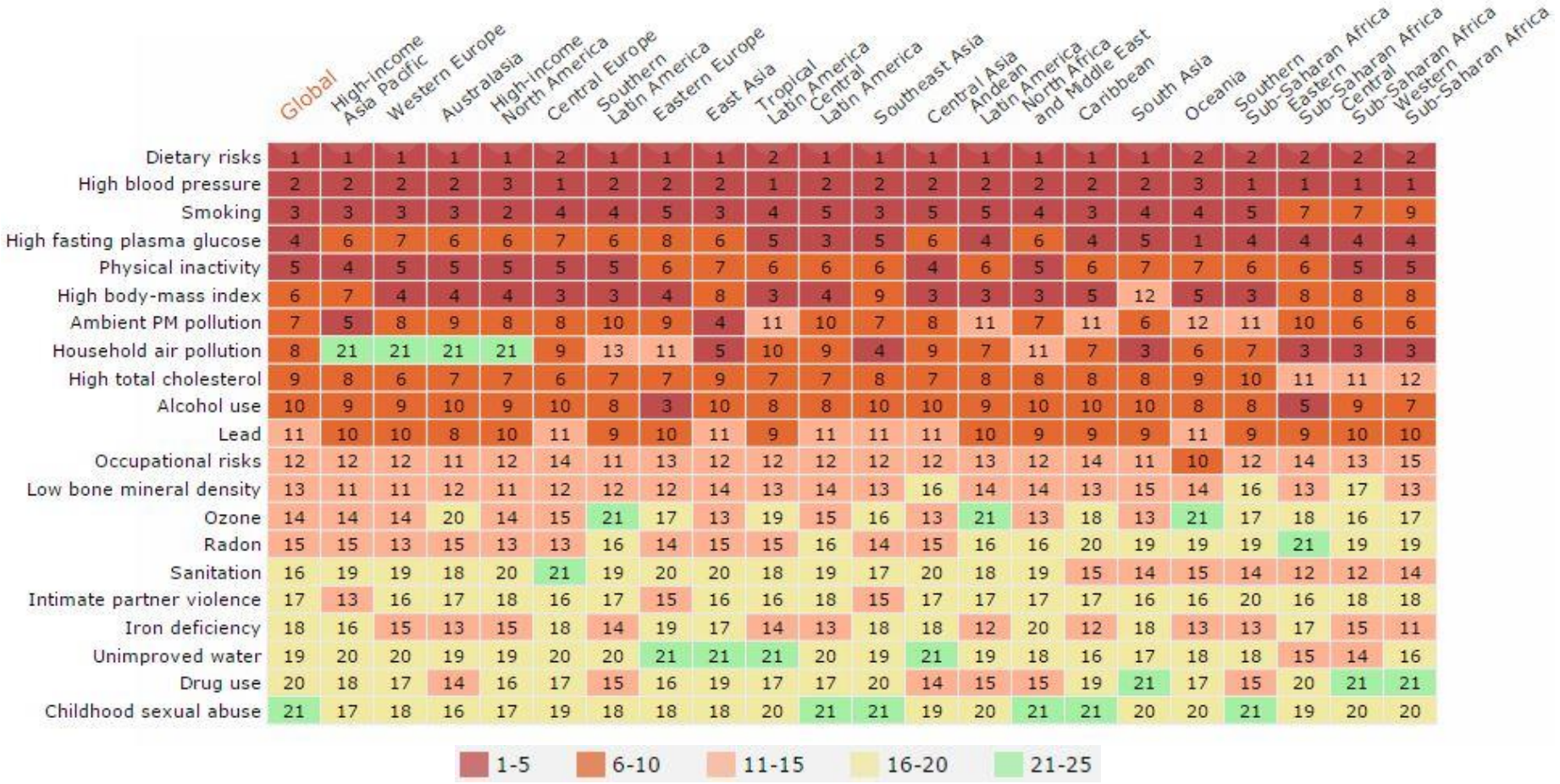

Figure 4.17. Ranking of Years of Life Lost due to premature mortality (YLLs) for all risk factors (ages ≥ 70, both sexes, 2010).

From Institute for Health Metrics and Evaluation (IHME) website; open acces and reproduction. (www.healthdata.org/gbd)

5 DISCUSSION

5.1 Discussion

Osteoporosis is a systemic skeletal disease in which bone strength is deteriorated with a subsequent increased risk of fracture. The consequences of osteoporotic fractures range from pain and disability to chronic institutionalization and death, with tremendous social and economic costs, which often exceed those resulting from other common conditions. The improvements in life expectancy and the massive growth of the ageing population in the world have predicted an enormous rise in the number of fractures worldwide, becoming one of the major epidemics in the following decades. Health initiatives are urgently required in order to promote early diagnosis and treatment, which has proven to be cost-effective. However, awareness of the disease is still very insufficient among individuals, health professionals and scientific institutions.

In the scope of the GBD 2010 study, low BMD was taken into account, for the first time, in the global health burden estimates. Given the complexity of measuring osteoporosis per se, low BMD was selected as a risk factor given its well established relationship with osteoporotic fractures and its relatively ease of measurement with standard techniques. Simultaneously, bone fractures were not analysed as a disease or condition and instead, included in the burden of falls within the injury group estimates. Hence, comparative risk assessment (CRA) methodology was used to estimate the population attributable fraction of falls burden due to low levels of BMD. Bone mineral density measured at FN by DXA was chosen as the exposure variable for the risk assessment with fractures because of data reliability and availability of

epidemiological data. Finally, systematic review, survey-derived DWs and hospital data were used to define relationship between falls and fracture-related morbidity and mortality.

Our results showed that, although age-adjusted data demonstrated an improving trend of the global BMD values over time, the absolute burden of low BMD increased from 1990 to 2010, probably related to the global growth of the aged population. Higher age-standardized rates of DALYs and PAFs in developing regions probably reflected the importance of the potentially modifiable determinants of low BMD (such as nutritional factors and access to health care). Premature mortality (YLLs) had slightly more contribution in the global DALYs than YLDs. This finding is partially explained by the major contribution of deaths in the overall burden, given that low BMD was responsible for at least one-third of all the deaths attributable to falls, which were the second (following road injuries) and the first cause in the list of injuries with the major global health burden in population 50-69 years and 70 years and above, respectively (http://www.healthdata.org/gbd) (Murray, Vos et al. 2012).

For all burden estimates, males showed higher values than females despite of the finding of higher PAFs of low BMD for falls for females than for males. One of the reasons for this was the higher fracture incidence in males than in females. Another reason was the higher mortality following a fracture in males compared to females, particularly at younger age groups, which is compatible with previous observations in longitudinal studies (Center, Nguyen et al. 1999; Kannegaard, van der Mark et al. 2010; Melton, Achenbach et al. 2013). The higher PAFs for falls in females

compared to males might have seem contradictory at the view of preliminary analysis of PAFs of low BMD for fractures (higher in males) (Figure 3.3 and Figure 3.4). However, falls burden represented a greater percentage of the overall health burden in females compared to that in males for both 1990 (13.93% vs 11.19%) and for 2010 (16.71% vs 13.51%), and therefore PAFs for falls (in contrast to PAFs for fractures) were higher in females that in males when sexes were analysed separately. The selection of all sites of fractures, including those not clearly related to osteoporosis (e.g. face, skull and finger), and the broad spectrum of the falls sub-causes for our estimations (including high energy injuries) is the most likely explanation behind the higher health burden of low BMD in males compared to females, together with the relatively high impact of low BMD in males compared to females using the age- and sex-specific TMRED for the CRA analysis.

Low BMD ranked relatively low compared with other risk factors in the GBD 2010 study, albeit the ranking improved for estimates focused in population 50 years and over. However, the contribution of low BMD to the global health burden compared with other risk factors was little, and it is likely that the burden of osteoporosis was underestimated for several reasons.

First, the choice of an age and sex-specific TMRED masked the important role of age and sex in the fracture risk (Kanis, Johnell et al. 2001), and it may explain in part the relatively lower health burden of BMD compared with other risk factors. Given that the gradient of risk of fracture for each unit of BMD decrease is the same in both men and women (Johnell, Kanis et al. 2005), the use of the young female reference

seems reasonable in clinical settings to decide whether intervention is recommended in individual subjects. Yet, the GBD study has the ultimate goal of providing useful information to establish health priorities; public health preventive campaigns are suitable for *modifiable,* in contrast to *non-modifiable,* risk factors. In consequence, sex and age should be taken out of the analysis if they are found to be independently related to the risk factor, and such is the case for low BMD. Moreover, in the CRA methodology, the TMRED should be theoretically possible at the population level by clear epidemiological evidence (Ezzati, Hoorn et al. 2011). Longitudinal studies (Burger, de Laet et al. 1998; Cauley, Lui et al. 2009) have demonstrated that a small percentage of older people can maintain their bone mass over the time in the absence of risk factors for osteoporosis. Cauley *et al* studied a cohort of 8224 women 65 years of age and older recruited at four clinical centres in the U.S. followed for 15 years (Cauley, Lui et al. 2009); a small percentage (9%) of the women maintained their BMD at the hip during the follow up period. Authors found that factors known to influence BMD, such as smoking, weight loss, physical activity and calcium intake, were more favourable in the *maintainers* group than in those women who experienced expected or accelerated bone loss. However, the extent to which the differences in BMD observed by age are modifiable at a population level is not certain. Furthermore, population-based studies in different parts of the world have demonstrated the opposite, showing different degrees of bone loss in older adults for all age groups, and faster rates of bone loss after menopause in females compared to age-matched males (Jones, Nguyen et al. 1994; Burger, de Laet et al. 1998; Yoshimura, Kinoshita et al. 2002). The finding of a BMD-maintainer group by Cauley et al supported our approach to use the sex- and age-specific 90th percentile

from the reference population (whites from NHANESIII) (Looker, Wahner et al. 1998), but extending the maintenance rule from the young reference was not supported by any valid scientific evidence, and seemed rather unrealistic. In spite of all these observations, we tested a PAFs model using young female reference for few regions with numerous data points (Western Europe, North America and Asia East). This approach led to negative PAFs for men up to the seventh decade, which is essentially contradictory in the CRA analysis; that is a risk factor cannot be protective even at the lowest population exposure possible and therefore, values are not meant to be below zero. Given the observation that a significant genetic component is as well related to the ability to retain bone mass (Arden and Spector 1997; Harris, Nguyen et al. 1998), the 90^{th} percentile (instead of 95^{th} or 99^{th} percentiles) was considered, albeit arbitrary, feasible.

The use of regional versions for the TMRED were considered, however an international reference was chosen in order to enable worldwide comparisons, and to follow the current recommendation for T scores calculations by the International Osteoporosis Foundation, the World Health Organization and the International Society for Clinical Densitometry (Kanis 2008; Kanis, McCloskey et al. 2008; Internaional Society of Clinical Densitometry 2013). The choice of a white American reference (Looker, Wahner et al. 1998) could lead to the assumption that the burden of low BMD might have been overestimated or underestimated depending on the world region. In reality, in NHANES, different cohorts have shown significant variations in their age-and sex-adjusted levels of BMD depending on their ethnicity (Looker, Wahner et al. 1998; Looker, Melton et al. 2009). Nonetheless, in the Study

of Women's Health Across the Nation (SWAN study), a multi-centre multi-ethnic longitudinal study in the U.S., has recently shown how little ethnicity differences in BMD explain the variations in fracture risk across African–American, Caucasian, Chinese, and Japanese (Ishii, Cauley et al. 2012). Instead, these authors found that composite indices measuring hip geometry and other parameters rather than low BMD alone, were responsible for a large inter-ethnicity variation in the fracture risks, which were consistent with those reported previously in a large cohort of almost 200,000 American women from 5 different ethnic groups (Barrett-Connor, Siris et al. 2005). On the other hand, the SWAN study had previously pointed out the role of anthropometric and lifestyle factors (Finkelstein, Lee et al. 2002) in the observed BMD racial differences, and so have other large studies (Barrett-Connor, Siris et al. 2005; Looker, Melton et al. 2009; Nam, Kweon et al. 2013; Araujo, Yang et al. 2014), including socio-economic status(Araujo, Yang et al. 2014). Interestingly, despite the existence of data supporting the role of poverty levels on BMD in different world regions (Shatrugna, Kulkarni et al. 2005; Amiri, Nabipour et al. 2008; Brennan, Henry et al. 2009; Brennan, Henry et al. 2010; Araujo, Yang et al. 2014), our study did not find any value of the lag-distributed income per capita to predict BMD, likewise for mean BMI and availability of milk. This probably indicates the complex multi-factorial nature of variables affecting BMD in different world regions. In the present study, for example, estimates on the population levels of BMD in Caribbean region, despite being a low income region, were higher both in men and women compared with most of the high income countries.

The potential impact of the global improvement of nutritional status and body size over the last 20 years was not reflected by selecting two different TMRED, one for 1990 and another one for 2010. Personal communication was established with the main bone investigator in NHANES initiative (Looker, AC) to obtain data from NHANES 2005-2008, as preliminary publications from such study had shown a general improvement in the population levels of BMD (Looker, Melton et al. 2012), thought to be at least partly related to factors such as body size, calcium intake and non-smoking. Unfortunately, at the time of this present study, age- and sex-specific 90^{th} percentiles of FNBMD from this most recent cohort were still not ready. Additionally, differences in FNBMD from the 1988-1994 survey (NHANES III) were less than 3% and thus, not appearing as crucial factor to take into account in our estimates. What is more, NHANES III is the reference used in the meta-analysis from which we derived the risk relationship between BMD and fractures (Johnell, Kanis et al. 2005), and therefore, it was reasonable to use the same cohort for the TMRED. Posterior studies after such MA published in 2005 have found comparable values on the relationship BMD-fractures and the RR values have not been updated yet in the FRAX® tool.

Beside all these considerations in regards to the choice of TMRED for our CRA analysis, what is important to highlight is that the risk relationship between BMD alone and fracture risk is comparable among ethnicities. In a very eloquent exercise, Leslie showed how using FNBMD that was average for ethnicity or average for white females minimally altered the FRAX® output in any ethnicity (Leslie 2012). The

same BMD-fracture homogeneity across ethnic group has recently been shown in older men (Shin, Zmuda et al. 2014).

Separating deaths due to specific fractures from the overall deaths due to falls was not straightforward. In the GBD 2010 study, injuries were classified in the cause list according to the external cause such as a road injury or self-harm, whereas the outcomes after the injury were determined by the nature of injury such as brain trauma or spinal cord transection (Vos, Flaxman et al. 2012). Hence, burden due to fractures was part of the total health burden due to falls. Hospital data with dual coding of discharges by external cause and nature of injury was the only available quality data to elucidate how many fracture-related deaths and disability were attributable to falls. Selecting population 50 years and over with hip and non-hip vertebra fractures non-including head or internal injuries served a double purpose. On one hand, acted as a *proxy* for osteoporotic or fragility fracture (particularly the exclusion of internal injury); on the other hand, facilitated the mortality analysis due to the fracture event itself (head injuries can easily lead to dramatic consequences without the event of a skull fracture, such as an intracranial cerebral haemorrhage). Our review did not find solid data on mortality due to falls-related fractures covering both sexes and all ages over 50 years old. Most of the studies reporting deaths from falls-related fractures had been done retrospectively from medical charts and death certificates, or they were restricted to old frail populations. The European Prospective Osteoporosis Study (EPOS) had reported incidence of falls and incidence of fracture-free falls for a large cohort of almost 15,000 men and women aged 50–79 years recruited from population-based registers in 30 European centres

and followed-up for a mean of 3 years (Roy, Pye et al. 2002). This study could have helped, albeit with some limitations such as the recall bias (i.e. fracture-free individuals are less likely to report a fall event), to elucidate what percentage of all falls in a population led to a fracture-related death. However, no mortality data on falls-related deaths had been published from EPOS cohort at the moment of our mortality estimations. A very recent extensive report from the IOF on osteoporosis in the European Union has published statistics on fracture-incidence and fracture-related deaths for most of the countries in the EU (Strom, Borgstrom et al. 2013; Svedbom, Hernlund et al. 2013). Number of deaths within the first year after the fracture have been collected over the last years by the IOF European Review Group through literature review, official statistical bureaus and personal communications. While this represents a very valuable effort to summarize the health and economic burden of osteoporotic fractures in Europe, it still leaves the issue of identifying the fall-related fracture death unresolved. Continuous communication was established with the leaders of the IOF, including personal meetings with its president John A Kanis, although no final consensus was reached in regards to this point. In conclusion, identifying falls-related deaths attributable to fragility fractures was very tedious with the current available data, and we accept that this is one of the potential sources of burden underestimation due to low BMD.

Contrary to the notion that most of the fracture burden is related to disability levels (most of subjects don't die after suffering a fracture), YLLs contributed in higher proportion to the global DALYs attributable to low BMD than YLDs. A plausible explanation for this is the very low DW assigned for long-term treated hip fracture

(Table 3.6). It is possible that the wording of the lay description (which included the term “fixed”) had induced a falsely optimistic result from the population surveys from which DWs were derived. Another possible source of missing data for YLDs is the predominant use of hospital data for falls-related fracture incidence, given the likelihood of non hospital consultation in case of minor fractures, particularly in non-developed regions.

Assuming that only accidental falls-related fractures were associated with low BMD has missed part of the potential health burden attributable to this risk factor. In the GBD 2010 study, risk factors such as high blood pressure and smoking were analysed assessing their impact on different outcomes: among others, ischaemic heart disease, ischemic and haemorrhagic stroke, chronic kidney disease, and atrial fibrillation for high blood pressure, and chronic respiratory diseases, ischaemic heart disease, and several cancer types for smoking (Lim, Vos et al. 2012). In contrast, only falls-related fractures in population 50 years and over (where we thought we would find most of osteoporotic fractures) were taken into account for the low BMD analysis, which went against previous studies showing the important role of BMD in both low-energy and high-energy trauma (Karlsson, Hasserius et al. 1993; Sanders, Pasco et al. 1998; Mackey, Lui et al. 2007), even in young population. One prospective study in subjects 65 years and older, with 8022 women from the Study of Osteoporotic Fractures and 5995 men from the Osteoporotic Fractures in Men Study (Mackey, Lui et al. 2007) showed that total hip BMD was associated with an increased risk of high-trauma fracture that was comparable to the risk of low trauma both in men and women (around 50% higher risk both for low- and high-energy

traumas for each 1 SD decrease in total hip BMD). Then, if we consider, for example, all fractures involved in road injuries and self-harm (first and second cause of injuries-related health burden globally, respectively), the potential percentage of low BMD burden that we may have left out is immense. Not to mention that road injuries were in the top ten rank of global health burden for 2010 among 291 conditions analysed in the GBD 2010 study and it showed an increasing trend from 1990.

On the other hand, only clinical fractures (those resulting from falls) accounted for fracture estimates for the GBD 2010 study, while it is well known that symptomatic vertebral fractures only represent about one third of all radiographically diagnosed spine fractures (Ross 1997). Vertebral compression fractures, even if occurring without acute symptoms, frequently involve long-term consequences such as chronic back pain, kyphosis and restrictive respiratory disease (Silverman 1992; Ross 1997). We expected the health burden of such radiographic spine fractures to be included in the low back pain estimates, admitting their exclusion from the falls burden, and therefore, decreasing the population attributable fraction of low BMD for fractures and consequently for falls.

The exclusion of all fractures locations other than hip and vertebra from fracture-related deaths analysis would also have contributed to the underestimation of the mortality burden attributable to low BMD. Hip fractures and clinical vertebral fractures have been shown to be the first and second most important sites for osteoporotic fractures-related deaths, respectively (Browner, Pressman et al. 1996; Bliuc, Nguyen

et al. 2009; Ioannidis, Papaioannou et al. 2009). For our mortality analysis, we used in-hospital data, and other fracture types were excluded as these were less likely to be the underlying cause of death, as shown in the Australian mortality database. (http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3303.0Main+Features 12003?OpenDocument). This finding was observed as well in the Canadian Multicentre Osteoporosis Study (CAMOS), a population-based study with 2187 men and 5566 women aged 50 years and older (the same age scope of this present analysis), where 5-year mortality risk was only increased after hip and vertebral fractures (Ioannidis, Papaioannou et al. 2009). The Study of Osteoporosis Fractures in U.S. had found similar results 10 years earlier (Cauley, Thompson et al. 2000) during a 3.8-year follow-up. However, other authors have observed that other osteoporotic fracture sites are related to a higher risk of long-term mortality compared with age and gender-matched peers (Bliuc, Nguyen et al. 2009; Morin, Lix et al. 2011; Melton, Achenbach et al. 2013). A prospective population-based study conducted over a 18-year period in Australia, the Dubbo Osteoporosis Epidemiology Study (DOES), showed that the fall-fracture event was likely to be missed out as an underlying cause for some deaths that occurred long time after the fall, particularly in non-hip and non-vertebral fractures (Bliuc, Nguyen et al. 2009). The study shows that non-hip non-vertebral fractures are responsible for one fourth of all fracture-related excess mortality for the first 5 years post-fracture (Bliuc, Nguyen et al. 2009; Bliuc, Nguyen et al. 2014). Mortality is higher in individuals over 75 years old compared to the 60-74 year group, and in major osteporotic fractures (pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus). But half of the excess mortality is attributable to the risk of subsequent fractures with high

burden such as hip fracture. And in actual fact, long-term mortality following fractures is tedious to interpret within the GBD study scope, particularly when the risk of death is very intrinsically associated with the risk of future fractures. Moreover, previous studies have demonstrated that mortality is highly related to baseline frailty (Cawthon, Marshall et al. 2007; Ensrud, Ewing et al. 2007; Tosteson, Gottlieb et al. 2007; Patel, Brennan et al. 2014), and it is hard to estimate which percentage of the long-term excess mortality is really due to the fracture event.

As the exposure variable measurement, DXA is considerably more expensive and technically more complicated than measurement systems for other risk factors such as high blood pressure or body mass index. Consequently, the availability for DXA scans is limited (International Osteoporosis Foundation 2008), leading to a selection bias towards countries with better access to DXA scanning systems. Furthermore, the application of standardization equations among different DXA manufacturers (Lu, Fuerst et al. 2001) is unlikely to have removed all differences, especially between models in the same manufacturer (Barthe, Braillon et al. 1997; Henzell, Dhaliwal et al. 2003).

Selecting the FN as the only location for the exposure variable measurement might have further underestimated the prevalence of low BMD, given the observation that T scores at lumbar spine tend to be lower than in FN when patients are screened for osteoporosis, sometimes leading to different WHO classification categories (the so-called *diagnostic discordance)* (Woodson 2000; O'Gradaigh, Debiram et al. 2003; Looker, Melton et al. 2012). In addition, despite BMD at femoral neck being a good

predictor of fracture risk for both hip and non-hip fractures, the best predictive value for vertebral fracture is found when BMD is measured at lumbar spine and not at the hip (Marshall, Johnell et al. 1996). Discordance, although to a much lesser extent, has also been found between hips in the same individual. The reasons behind the differences in hip and spine BMD are thought to be diverse, some of them due to known physiological mechanisms. Trabecular bone, found in more proportion in the lumbar spine, is known to lose mineral content more rapidly in comparison with cortical bone, which is found in higher proportion in the neck of the femur (Watts 2004). The density of the bone also changes depending on the site, with the spine reaching peak at least 5 years before the hip (Blank, Malone et al. 2006)**.** Many secondary osteoporosis, such as glucocorticoid-induced, tend to affect trabecular bone first, leading to higher prevalence of lumbar osteoporosis (Cooper, Syddall et al. 2005). However, osteoarthritic changes, vascular calcifications and old vertebral fractures can falsely increase BMD in the spine, and need to be interpreted with caution in clinical settings. In contrast, the measurement of BMD at FN is rarely affected by these artefacts, and therefore, constitutes a more objective measurement of bone mass (Paggiosi, Glueer et al. 2011). Furthermore, until now, the most robust epidemiological data in the risk relationship between BMD and fracture uses FNBMD as the exposure variable (Johnell, Kanis et al. 2005).

This study is focused in the potential health burden of low BMD, which despite being well correlated with fracture risk and being one of the strongest predictors of osteoporotic fracture, has low sensitivity by itself in identifying absolute fracture risk (Siris, Chen et al. 2004). Measuring BMD alone provides with a quantitative value

not accounting for other anatomical and mechanical properties of the bone known to influence bone strength, and consequently, leading to an underestimation of the burden associated with osteoporosis. It is possible that future research may include composite measures of bone strength that include not only BMD, but also hip geometry parameters, thickness of cortical and trabecular bone, etc. For now, this is not applicable at a population level for a global analysis. Still, for health burden estimates, we defend assessing BMD as a continuous variable rather than osteoporosis as per WHO categorical definition (which is based on BMD only), as it's been done in another recent work (Oden, McCloskey et al. 2013).

As per the quality of the studies finally included from the SR, selection bias in some of the selected studies was a potential source of bias. Most of the studies excluded subjects with prior history of fracture, with bone metabolism diseases, or those receiving treatments that might affect bone metabolism. We expected to find discrepancies in the BMD values among different study groups depending on the exclusion or inclusion of such subjects, but linear regression models failed to prove such assumption. Reasons for this are not fully apparent, but it might be related to the heterogeneity among studies and the relatively low number of studies for each bias group. These authors recommend including individuals with previous fractures or diagnosed bone disease in similar future studies. This is particularly important in elderly populations, as the percentage of individuals with a history of previous fragility fractures is high, and excluding such subjects makes the sample not truly representative of the real population and underestimates the real risk.

Finally, it is important to remember that the GBD initiative does not take into account the social loss and the economic burden due to the different health causes. As shown in section 1.4 *Economic Cost of Osteoporotic Fractures*, osteoporotic fractures involve an enormous economic cost for most of the word regions, and it's predicted to keep growing in the following decades due to the ageing of the global population. Screening of osteoporosis and pharmacological treatment to increase BMD and reduce fracture risk is relatively cheap and clearly cost-effective (refer to section 1.6.3 *Major pharmacological interventions*). Moreover, the cost-effectivity is well supported in advanced ages, which is not always the case for other risk factors such as hypertension or hypercholesterolemia, which seem to reach a plateau with the age (Zethraeus, Strom et al. 2008). Therefore, all these important factors should be considered by public health authorities when deciding on health priorities and allocating resources, and not simply the top rank of conditions causing the major health burden.

6 CONCLUSIONS

This study is the first of its kind in measuring the health burden attributable to low BMD as a continuous variable from a global perspective, enabling estimates comparisons among different world regions, countries, age groups, sexes, and time periods. The main conclusions of the study are as follow:

1. Asia and Africa were the world regions with the lowest values of FNBMD among population 50 years and over, while High-Income North America, Caribbean and Eastern Europe showed the highest FNBMD values both for men and women. Although age-adjusted data showed an improving trend of the global FNBMD values between 1990 and 2010, especially in Asia and Western Europe, FNBMD at a population level decreased in some regions due to the ageing of the population. As expected, population levels of FNBMD were lower in females than in males for both time periods.
2. Population attributable fractions (PAFs) of low BMD for falls were generally higher for females compared to males both for 1990 and 2010. In general, world regions with low GDP showed the highest PAFs (Asia East and South-East, Sub-Saharan Africa East and West), with the exception of Eastern Europe. However, big disparities in PAFs were observed among high income countries, even within the same world region. Global PAFs of low BMD for falls increased from 1990 to 2010 both for males and females. In 1990 global DALYs and deaths attributable to low BMD constituted 12.1% and 29.6% of all falls-related DALYs and deaths, respectively. These percentages increased to 14.8% and 34.7%, respectively, for 2010 estimates
3. The percentage of low BMD in the total global health burden almost doubled from 1990 (0.12%) to 2010 (0.21%). In population aged 50-69 years, such

percentages increased to 0.41% for 1990 and 0.5% for 2010, and were even higher in population aged 70 years and above (0.64% and 0.79%, respectively). The fraction of the total regional burden increased in most of world regions.

4. Global deaths attributable to low BMD increased from 103,000 in 1990 to 188,000 in 2010. Deaths attributable to low BMD almost doubled in males from 1990 to 2010, from 52,816 to 103,440, while in females they increased around 60% between both time periods, with 50,455 and 84,146 deaths in 1990 and 2010, respectively. Around one third of all falls-related deaths occurring in the world were attributable to low BMD.
5. Global DALYs attributable to low BMD increased from 3,125,000 in 1990 to 5,216,000 in 2010 respectively. Asia East and South were the major contributing regions to the increase of the global burden of low BMD likely due to the growth of the ageing population and the relatively low population levels of BMD compared with other world regions. Rates of global DALYs per 100,000 were higher in developed regions, while the highest age-standardized rates were in developing regions. For all time periods, YLLs contributed to the global burden of low BMD slightly more than YLDs, representing 51% and 53% of all DALYs for 1990 and 2010, respectively. Males obtained more DALYs than females for the analysed time periods, with a gap between both sexes that increased from 1990 to 2010, with 56% and 60% of all DALYs corresponding to males for 1990 and 2010, respectively.
6. Low BMD had a relatively low weight in the global burden compared to other risk factors in the GBD 2010 study. It ranked 20th among 21, and 23rd among 25 risk factor categories globally for 1990 and 2010, respectively. By region,

the highest rankings were observed in developed regions. By age group, the highest ranking was found in population 70 years and over, moving to the 11th position out of 17 risk factors categories for 1990 and to the 13th position globally out of 21 for 2010. Similar positions were found for females and males.

7 FUTURE PERSPECTIVES

The contribution of low BMD to the global health burden compared with other risk factors was little, and it is likely that the burden of osteoporosis was underestimated for several reasons, as discussed previously. To improve the estimates of the health burden of low BMD in fractures and falls, the osteoporosis working group for the ongoing GBD 2013 study, which the author of the present thesis is part of, is updating the burden estimates by:

1) Incorporating new epidemiological data from updated systematic review on population levels of bone mineral density, including as well young adults from 20 to 50 years of age.
2) Updating reference values for the TMRED from most recent NHANES data.
3) Including all kind of injuries with a fracture as an outcome and not only falls, such as road injuries, non-venomous animal contact, assaults and exposure to forces of nature. The inclusion of road injuries, particularly, will represent a great contribution to increase the estimated health burden due to low BMD, as preliminary data has shown.
4) Looking for reliable epidemiological data assessing risk relationship of BMD and fractures in young adults.
5) Evaluating the inclusion of non-hip non-vertebra fractures in the mortality burden due to low BMD.

The last two points mentioned above are offering some difficult challenges to the research team: First, no prospective population-based studies have been found to solidly establish a relationship between BMD and fractures in population younger than 50 both for men and women, even after personal communication with worldwide

experts. It might be possible to extend the estimates to population aged 40 to 50 years, particularly in women, but for the moment, it seems there is no epidemiological data to calculate burden of low BMD in younger adults. Second, the inclusion of non-hip non-vertebra fractures in mortality estimates is still under debate. This is because great part of the excess mortality derived from such fractures is consequence of the long-term risk of suffering a hip or a vertebra fracture, and therefore, there is still a difficulty to causally relate the mortality burden to the first fracture event.

Future endeavours in the GBD initiative might consider to include “osteoporosis” as a disease, rather than (or apart from) low BMD as a risk factor. Yet, methodology should be able to overcome some important challenges, such as the lack of osteoporosis coding in most of the death certificates for fractures-related deaths.

Considering that the risk of fracture due to reduced BMD is gradual over a continuum, and the important epidemiological weight of fractures occurring in patients with osteopenia, future approaches should still be based in BMD as a continuous variable, rather than studying osteoporosis based in the WHO definition of T score of -2.5 or below.

Most recent technologies in bone imaging, such as high-resolution quantitative computed tomography (HR-QTC), micro-computed tomography and, particularly, trabecular bone score (TBS) from DXA, might be used in the future to thoroughly assess bone strength not only considering BMD, but also bone microarchitecture. Nevertheless, there is insufficient data for the moment to use such techniques for the

GBD study estimates, which require a reasonable amount of epidemiological data. In the future, incorporating information on bone architecture will probably improve the fracture prediction algorithms and may allow to assess the global health burden of *osteoporosis* as a disease rather than low BMD alone as risk factor.

Health information systems and health professionals should be better prepared to detect fragility fractures and long-term mortality related to them. Nature of injuries (e.g. fracture) should be coded together with the cause of the injury (e.g. fall) for early detection of osteoporotic fractures. This might require a change in the ICD coding system. Widespread use of electronic record systems around the world could be useful tool to detect individuals at high risk of fracture, and should be better equipped in order to improve screening and management of osteoporosis. The information provided can also be used to better plan public health prevention and management programs.

The MSK EG of the GBD 2010 study, in collaboration with the Bone and Joint Decade initiative, is currently collaborating with the WHO in order to increase recognition of the burden of MSK diseases, including low BMD and fragility fractures. In particular, background papers are currently being prepared to be part of the WHO health reports for ageing and frailty, as well as epidemiological data on disability is being collected in order to recognize the great role of MSK disorders in the overall disability levels of non-communicable diseases.

8 APPLICABILITY

Our project provides a unique methodology that enables comparison of the health burden of low bone mineral density among different world regions, age groups and genders, and the ability to analyse time trends.

- It provides standardized quantification of the burden (DALY's, deaths, YLLs, YLDs) that can be reproducible in future studies.
- It highlights areas where the methodology could be modified for future analyses.
- It expresses the burden of low bone mineral density as a fraction of the health burden due to falls, which has not been calculated previously in the context of all other diseases and risk factors.
- This research project is part of an important international initiative with world experts in global epidemiology and expert leaders in the corresponding fields. The four core papers of the GBD 2010 study were already published in Lancet in 2012, and the new updates from the GBD 2013 study will be published in 2015. Multiple disease-focused manuscripts and regional reports have been published. The GBD initiative is present in the main international medical conferences, in newspapers, in TV programs, and in university lectures around the world. It represents an ongoing global network to facilitate the awareness of the burden of the different conditions and risk factors in the world, both to scientific and non-scientific audiences.
- Our estimates can provide useful information for health authorities and policy makers, and can be helpful for future population campaigns for osteoporosis screening and management.

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10 APPENDICES

Appendix 1. Global Burden of Disease Countries Listed by Region

GBD Country by Region
ASIA PACIFIC, HIGH INCOME
Brunei Darussalam
Japan
Republic of Korea
Singapore
ASIA, CENTRAL
Armenia
Azerbaijan
Georgia
Kazakhstan
Kyrgyzstan
Mongolia
Tajikistan
Turkmenistan
Uzbekistan
ASIA, EAST
China
Democratic People's Republic of Korea
Hong Kong
Macao
Taiwan
ASIA, SOUTH
Afghanistan
Bangladesh
Bhutan
India
Nepal
Pakistan
ASIA, SOUTHEAST
Cambodia
Christmas Island
Cocos Islands
Indonesia
Lao People's Democratic Republic
Malaysia
Maldives
Mauritius
Myanmar
Philippines
Reunion
Seychelles
Sri Lanka

GBD Country by Region
Thailand
Timore Leste
Viet Nam
AUSTRALASIA
Australia
New Zealand
CARIBBEAN
Anguilla
Antigua and Barbuda
Aruba
Bahamas
Barbados
Belize
Bermuda
British Virgin Islands
Cayman Islands
Cuba
Dominica
Dominican Republic
French Guiana
Grenada
Guadeloupe
Guyana
Haiti
Jamaica
Martinique
Montserrat
Netherlands Antilles
Puerto Rico
Saint Barthelemy
Saint Kitts and Nevis
Saint Lucia
Saint Martin
Saint Vincent and the Grenadines
Suriname
Trinidad and Tobago
Turks and Caicos Islands
US Virgin Islands
EUROPE, CENTRAL
Albania
Bosnia and Herzegovina
Bulgaria
Croatia
Czech Republic

GBD Country by Region
Hungary
Montenegro
Poland
Romania
Serbia
Slovakia
Slovenia
The Former Yugoslav Republic of Macedonia
EUROPE, EASTERN
Belarus
Estonia
Latvia
Lithuania
Republic of Moldova
Russian Federation
Ukraine
EUROPE, WESTERN
Akrotiri and Dhekelia
Aland Islands
Andorra
Austria
Belgium
Channel Islands
Cyprus
Denmark
Faeroe Islands
Finland
France
Germany
Gibraltar
Greece
Greenland
Guernsey
Holy See
Iceland
Ireland
Isle of Man
Israel
Italy
Jersey
Liechtenstein
Luxembourg
Malta
Monaco

GBD Country by Region
Netherlands
Norway
Portugal
San Marino
Spain
Svalbard
Sweden
Switzerland
United Kingdom
LATIN AMERICA, ANDEAN
Bolivia
Ecuador
Peru
LATIN AMERICA, CENTRAL
Colombia
Costa Rica
El Salvador
Guatemala
Honduras
Mexico
Nicaragua
Panama
Venezuela
LATIN AMERICA, SOUTHERN
Argentina
Chile
Falkland Islands (Malvinas)
Uruguay
LATIN AMERICA, TROPICAL
Brazil
Paraguay
NORTH AFRICA / MIDDLE EAST
Algeria
Bahrain
Egypt
Iran (Islamic Republic of)
Iraq
Jordan
Kuwait
Lebanon
Libyan Arab Jamahiriya
Morocco
Occupied Palestinian Territory
Oman

GBD Country by Region
Qatar
Saudi Arabia
Syrian Arab Republic
Tunisia
Turkey
United Arab Emirates
Western Sahara
Yemen
NORTH AMERICA, HIGH INCOME
Canada
Saint Pierre et Miquelon
United States of America
OCEANIA
American Samoa
Cook Islands
Fiji
French Polynesia
Guam
Kiribati
Marshall Islands
Micronesia (Federated States of)
Nauru
New Caledonia
Niue
Norfolk Island
Northern Mariana Islands
Palau
Papua New Guinea
Pitcairn
Samoa
Solomon Islands
Tokelau
Tonga
Tuvalu
Vanuatu
Wallis and Futuna Islands
SUB-SAHARAN AFRICA, CENTRAL
Angola
Central African Republic
Congo
Democratic Republic of the Congo
Equatorial Guinea
Gabon
SUB-SAHARAN AFRICA, EAST

GBD Country by Region
Burundi
Comoros
Djibouti
Eritrea
Ethiopia
Kenya
Madagascar
Malawi
Mayotte
Mozambique
Rwanda
Somalia
Sudan
Uganda
United Republic of Tanzania
Zambia
SUB-SAHARAN AFRICA, SOUTHERN
Botswana
Lesotho
Namibia
South Africa
Swaziland
Zimbabwe
SUB-SAHARAN AFRICA, WEST
Benin
Burkina Faso
Cameroon
Cape Verde
Chad
Cote d'Ivoire
Gambia
Ghana
Guinea
Guinea-Bissau
Liberia
Mali
Mauritania
Niger
Nigeria
Saint Helena
Sao Tome and Principe
Senegal
Sierra Leone
Togo

Appendix 2. GBD 2010 Musculoskeletal Disorders Risk of Bias Tool to Check Study Quality: Osteoporosis Exposure and Fracture Risk Relationship

Name of author(s): _____ Year of publication: _____

Name of paper/study: _____

Quality Item	Criteria for answers	Additional notes	Answer
1. Was bone mineral density shown for a clearly described anatomical location (femoral neck, spine, distal forearm)?	• **LOW RISK:** A clear anatomical location of the relevant region of the body was used in the study. • **HIGH RISK**: A clear anatomical location of the relevant region of the body was NOT used in the study. • **UNCLEAR:** There is insufficient information to permit a judgement of low or high risk.	For example: • A study where BMD was assessed in all individuals at **femoral neck**. The answer is: LOW RISK. • The article gives BMD values of the hip but doesn't specify the region (FN, Wards triangle, total hip, etc.). The answer would be UNCLEAR.	• **Low Risk** • **High Risk*** • **Unclear***
2. Was there a case definition that clearly described the measured outcome (**fracture or mortality**)?	• **LOW RISK:** A case definition for fractures was used in the study **OR** the outcome to measure is deaths. • **HIGH RISK**: A case definition for fractures was NOT used in the study. • **UNCLEAR:** There is insufficient information to permit a judgement of low, moderate or high risk.	A **<u>hip fracture</u>** is generally a fracture of the proximal femur. There are three types: femoral neck, intertrochanteric and subtrochanteric (just below the lesser trochanter). An osteoporotic **<u>DISTAL forearm fracture</u>** is the result of a low-impact trauma. It needs to involve the distal part of radius and/or ulna. There are 8 different types of distal forearm fractures (Frykman classification). In the ICD10 classification distal forearm fractures EXCLUDE fractures from the wrist and hand. An **<u>osteoporotic vertebral fracture</u>** is generally a fracture of the vertebra body due to a low-impact trauma or in the absence of specific trauma in **thoracic or lumbar spine**. The definition for a "prevalent" or "incident" fracture can vary among studies; thus, the values given are not directly "comparable.[1] For instance, some studies have defined a new fracture as > 15 % reduction in any one of the three measured vertebra heights compared to a previous X-ray; to reduce false-positive results, other investigators propose a more stringent criteria of 20% or more, and others suggest to combine the latest with an absolute loss of 4mm to increase specificity. For prevalence, the NOF suggests that in studies involving community populations, prevalence vertebral fractures be defined as a reduction of 3 SD or more below the normal dimensions for that particular vertebral level For example: • A study assessing femur fractures not specifying if they are proximal or shaft femur fractures. The answer is HIGH RISK. • The following case definition was used: "hip fractures were considered as	• **Low Risk** • **High Risk*** • **Unclear***

Quality Item	Criteria for answers	Additional notes	Answer
		proximal femur fractures resulting from a low-impact trauma. The answer is: LOW RISK. • The following case definition was used: "hip fractures were considered as proximal femur fractures occurring in individuals 50 years or older. The answer is: LOW RISK. • **A study assessing prevalence of vertebral fractures with lumbar X-rays (not including thoracic vertebrae). The answer is HIGH RISK.**	
3. Was the study instrument that measured the exposure to the risk factor (BMD) reliable AND valid?	• **LOW RISK:** The study instrument was reliable and valid. • **MODERATE RISK**: The study instrument was valid, but it was just moderately reliable. • **HIGH RISK**: The study instrument was not valid. • **UNCLEAR:** There is insufficient information to permit a judgement of low, moderate or high risk.	The study instrument used for measuring BMD is Dual-X-Ray-Absorptiometry (DXA). Other techniques to assess BMD are not eligible for this GBD study. For DXA techniques, the authors should report the manufacturer and the model used for the BMD measures and the site-specific coefficient of variation (COV). For example: • A study using DXA not reporting the manufacturer equipment or model. The answer is: UNCLEAR. • A study using DXA reporting the manufacturer equipment, the model and a COV <2.5%[2]. The answer is LOW RISK. • A study reporting the manufacturer and model, but no information on the COV is provided. The answer is: MODERATE RISK. • A COV between 2.5 and 3.5%. The answer is: MODERATE RISK[3]. • A study assessing BMD measures with a COV at FN >3.5% for an individual technologist. The answer is: HIGH RISK • A multicentric study reporting mean values of BMD assessed with different instruments without cross-calibration between facilities would be HIGH RISK.	• **Low Risk** • **Moderate Risk** • **High Risk** • **Unclear***
4. Was the assessment of the outcome (fracture or mortality) reliable?	• **LOW RISK**: The outcome is assessed through reliable data sources in all the subjects confirmed by radiological evidence (fracture) or by administrative record linkage (fractures or deaths). • **MODERATE RISK**: The outcome is assessed through reliable sources only in a part of the subjects, **OR**, the outcome is assessed only through chart review. • **HIGH RISK**: The outcome is not assessed through reliable data sources in most of the subjects. • **UNCLEAR**: There is insufficient information to permit a judgement of low, moderate or high risk.	There is a lower risk of bias if clinical outcomes like fractures or deaths are confirmed with radiology (fractures), clinical records or administrative data. For example: • A study that collects data on fractures only through the subjects (or a proxy) self-report. The answer is: HIGH RISK. • A study that collects data on fractures or deaths through chart review. The answer is: MODERATE RISK. • A study that collects data on fractures through subjects self report and confirms positive cases with an X-Ray report. The answer is: LOW RISK. • A study that collects data on mortality through subjects relatives or chart review and confirm cases with death certificate or administrative record linkage. The answer is: LOW RISK.	• **Low Risk** • **Moderate Risk** • **High Risk** • **Unclear**
5. Was the study's target population representative of the	• **LOW RISK:** The target population was a true representation of the national population. • **MODERATE RISK**: The target population	The target population of the study refers to the group of people or entities to which the results of the study will be generalised. This item focuses on whether the target population is representative of the national population.	• **Low Risk** • **Moderate Risk**

Quality Item	Criteria for answers	Additional notes	Answer
national population?	was a close representation of the national population. • **HIGH RISK**: The target population was clearly not representative of the national population. • **UNCLEAR:** There is insufficient information to permit a judgement of low, moderate, or high risk.	For example: • The study was a national health survey of people 20 years and over and the sample was representative of the national population aged 20 years and over. The answer is: LOW RISK. • The study was a provincial survey and the province was considered closely representative of the national population. The answer is: MODERATE RISK. • The study was conducted in one village only, which was clearly not representative of the national population. The answer is: HIGH RISK.	• **High Risk** • **Unclear**
6. Was the sampling frame representative of the target population?	• **LOW RISK:** The sampling frame was a true representation of the target population. • **MODERATE RISK**: The sampling frame was a close representation of the target population. • **HIGH RISK**: The sampling frame was a poor representation of the target population. • **UNCLEAR:** There is insufficient information to permit a judgement of low, moderate, or high risk.	The sampling frame is a list of the sampling units in the target population and the study sample population is drawn from this list. It is rare to obtain a complete list of all the sampling units; however, where possible, the sampling frame should be representative of the target population. For example: • The sampling frame was a complete list of every individual within the target population. The answer is: LOW RISK. • The sampling frame was an 'almost' complete list of every individual within the target population. The answer is: MODERATE RISK. • The cluster sampling method was used - the sampling unit was villages. All villages in the target population were included. The answer is: LOW RISK.	• **Low Risk** • **Moderate Risk** • **High Risk** • **Unclear**
7. Were randomised methods used to select the sample population?	• **LOW RISK:** Randomised methods were used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • **HIGH RISK**: Randomised methods were NOT used to select the sample. • **UNCLEAR:** There is insufficient information to permit a judgement of low or high risk.	The sample population is selected from the sampling frame. For example: • The sample population was selected using the cluster technique. The answer is: LOW RISK.	• **Low Risk** • **High Risk** • **Unclear**
8. Was there likely to have been non-response bias?	• **LOW RISK:** The response rate (participation rate) at baseline was >/=70%[4], **OR**, An analysis was performed that showed no significant difference in the variable of interest between responders and non-responders (people who did not wish to participate), **OR,** An adjustment was made to remove any effect of non-response bias. • **MODERATE RISK**: The overall response rate is <70 but >/=50% Most of the subjects in the sample are asked to undergo BMD testing. • **HIGH RISK**: None of the three scenarios listed in the above LOW RISK criteria	This response rate mentioned in this item relates to the study within which the parameter of interest was measured (e.g. BMD measures to assess osteoporosis prevalence). For example: • Although the overall response rate of the study was 48%, the researchers carried out an analysis and found no significant difference in the prevalence of osteoporosis/BMD measures between responders and non-responders. The answer is: LOW RISK. • The response overall response rate was 48% and the researchers did NOT carry out an analysis to compare the prevalence of low back pain between responders and non-responders NOR did they make any adjustment for non-response bias. The answer is: HIGH RISK.	• **Low Risk** • **High Risk** • **Unclear**

Quality Item	Criteria for answers	Additional notes	Answer
	existed, and the overall response rate was <50%. • **UNCLEAR:** There is insufficient information to permit a judgement of low or high risk.		
9. Was there adjustments for confounding factors when analyzing the relationship between BMD and the outcome (fractures)	• **LOW RISK**: The outcome is adjusted by other relevant clinical factors. • **MODERATE RISK**: The outcome is only adjusted by age and gender. • **HIGH RISK**: The outcome is not adjusted by any other clinical factor. • **UNCLEAR:** There is insufficient information to permit a judgement of low, moderate or high risk.	For example: • A study that analyzes the association between BMD and risk of fracture, making adjustments for age, sex, BMI and menopausal status. The answer is: LOW RISK. • A study that analyzes the association between BMD and risk of fracture or death only adjusting for age and gender. The answer is MODERATE RISK. • A study that analyzes the association between BMD and mortality with no adjustments for age, sex or other common risk factors (smoking, social status, diabetes, HTA, etc). The answer is: HIGH RISK.	• **Low Risk** • **Moderate Risk** • **High Risk** • **Unclear**
10. Was the follow-up period long enough for outcomes (fracture) to occur?	• **LOW RISK:** The follow-up period was adequate for the outcome of interest. • **HIGH RISK:** The follow-up period was not adequate for the outcome of interest. • **UNCLEAR:** There is insufficient information to permit a judgement of low or high risk.	The minimum follow-up period should be at least of 1 year.	• **Low Risk** • **High Risk** • **Unclear**
11. Was the follow-up cohort adequate to measure the outcome of interest (fracture)?	• **LOW RISK**: Most of subjects completed **longitudinal** follow-up, OR the number of lost subjects is small (<10)% OR the investigators provide description of the lost subjects and show the unlikelihood of bias. • **MOD RISK**: The number of lost subjects is >10 but <30%. • **HIGH RISK**: None of the scenarios listed above exists. • **UNCLEAR**: There is insufficient information to permit a judgement of low or high risk.	Retrospective cohorts for the assessment of fractures will be HIGH RISK.	• **Low Risk** • **Moderate Risk** • **High Risk** • **Unclear**
12. Was there risk of selection bias?	• **LOW RISK:** All **s**ubjects are included in the analysis. • **MODERATE RISK:** Subjects under bone supplements/treatment, diseases or therapies with impact on bone metabolism are excluded. • **HIGH RISK:** Subjects with prior fractures are excluded from the analysis. • **UNCLEAR**: There is insufficient information to permit a judgement of low or high risk.		• **Low Risk** • **High Risk** • **Unclear**
Reviewer's decision	• **LOW RISK:** Further research is very unlikely		• **Low Risk**

Quality Item	Criteria for answers	Additional notes	Answer
about the study's overall level of bias	to change our confidence in the estimate. • **MODERATE RISK:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. • **HIGH RISK:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.		• **Moderate Risk** • **High Risk**

[1]http://courses.washington.edu/bonephys/fxdef.html#def

[2]The minimum acceptable precision for an individual technologist is 2.5% for FN. Official positions 2007. The International Society for Clinical Densitometry: http://www.iscd.org/Visitors/pdfs/ISCD2007OfficialPositions-Combined-AdultandPediatric.pdf.

[3] After the use of the universal standardization formula between Hologic and Luna, the average error for an individual patient was of 3.5%, which is considered "clinical acceptable". Hui SL et al. Universal standardization of bone density measurements: a method with optimal properties for calibration among several instruments (1997). JBMR; 12:1463-70.

[4] That is the percentage after the response rate for the sampling + response rate to undergo BMD testing. For ex. 77% X 65% = 50% In NHANES III the response rate for BMD testing was about 86% (only BMD) and the overall response rate was between 62.10 (60 years old or older) and 77.19 (between 20 and 39 years old). The latest computed by the product of screened sample response rate, the interview sample response rate, and the examined sample response rate. Mohader,L et al. National Health and Nutrition Examination Survey II. Accounting for item nonresponse bias. (1994) Rockville, Maryland (USA).

Appendix 3. Cause of Fall Codes – International Classification of Diseases (ICD)-9 and -10 Codes

ICD-9 Codes for Causes of Fall Injuries

ACCIDENTAL FALLS (E880-E888)

Excludes: E890.8, E891.8 burning building
Excludes: E890.0-E899 into fire
Excludes: E910.0-E910.9 into water (with submersion or drowning)
Excludes: E919.0-E919.9 machinery (in operation)
Excludes: E920.0-E920.9 on edged, pointed, or sharp object
Excludes: E800.0-E845.9 transport vehicle
Excludes: E846-E848 vehicle not elsewhere classifiable

E880 Fall on or from stairs or steps

E880.0 Escalator

E880.1 Fall on or from sidewalk curb

Excludes: E885.9 fall from moving sidewalk

E880.9 Other stairs or steps

E881 Fall on or from ladders or scaffolding

E881.0 Fall from ladder

E881.1 Fall from scaffolding

E882 Fall from or out of building or other structure

Fall from: balcony, bridge, building, flagpole, tower, turret, viaduct, wall, window
Fall through roof

Excludes: E916 collapse of a building or structure
Excludes: E890.8, E891.8 fall or jump from burning building

E883 Fall into hole or other opening in surface

Includes: fall into: cavity, dock, hole, pit, quarry, shaft, swimming pool, tank, well

Excludes: E910.9 fall into water NOS resulting in drowning or submersion without mention of injury
Excludes: E910.0-E910.9

E883.0 Accident from diving or jumping into water (swimming pool)

Strike or hit: against bottom when jumping or diving into water, wall or board of swimming pool, water surface

Excludes: E913.2 diving with insufficient air supply
Excludes: E902.2 effects of air pressure from diving

ICD-9 Codes for Causes of Fall Injuries

E883.1 Accidental fall into well
E883.2 Accidental fall into storm drain or manhole
E883.9 Fall into other hole or other opening in surface
E884 Other fall from one level to another
E884.0 Fall from playground equipment
Excludes: E919.8 recreational machinery
E884.1 Fall from cliff
E884.2 Fall from chair
E884.3 Fall from wheelchair
E884.4 Fall from bed
E884.5 Fall from other furniture
E884.6 Fall from commode: Toilet
E884.9 Other fall from one level to another: Fall from: embankment, haystack, stationary vehicle, tree
E885 Fall on same level from slipping, tripping, or stumbling
E885.0 Fall from (nonmotorized) scooter
E885.1 Fall from roller skates: Inline skates
E885.2 Fall from skateboard
E885.3 Fall from skis
E885.4 Fall from snowboard
E885.9 Fall from other slipping, tripping, or stumbling
Fall on moving sidewalk
E886 Fall on same level from collision, pushing, or shoving, by or with other person
Excludes: E917.1, E917.6 crushed or pushed by a crowd or human stampede
E886.0 In sports: Tackles in sports
Excludes: E917.0, E917.5 kicked, stepped on, struck by object, in sports
E886.9 Other and unspecified: Fall from collision of pedestrian (conveyance) with another pedestrian (conveyance)
E888 Other and unspecified fall: Accidental fall NOS, Fall on same level NOS
E888.0 Fall resulting in striking against sharp object
E920 Use additional external cause code to identify object
E888.1 Fall resulting in striking against other object
E888.8 Other fall
E888.9 Unspecified fall: Fall NOS

ICD-9 Codes for Causes of Fall Injuries	
E929.3	**Late effects of accidental fall**
ICD-10 Codes for Causes of Falls Injuries	
W00	Fall on same level involving ice and snow
W01	Fall on same level from slipping, tripping, and stumbling
W02	Fall involving ice skates, skis, roller skates, or skateboards
W03	Other fall on same level due to collision with, or pushing by, another person
W04	Fall while being carried or supported by other persons
W05	Fall involving wheelchair
W06	Fall involving bed
W07	Fall involving chair
W08	Fall involving other furniture
W09	Fall involving playground equipment
W10	Fall on and from stairs and steps
W11	Fall on and from ladder
W12	Fall on and from scaffolding
W13	Fall from, out of, or through building or structure
W14	Fall from tree
W15	Fall from cliff
W16	Diving or jumping into water causing injury other than drowning or submersion
W17	Other fall from one level to another
W18	Other fall on same level
W19	Unspecified fall

Appendix 4. Disability Weights in the Global Burden of Disease 2010 Study

(Adapted from Salomon JA et al 2012 (Salomon, Vos et al. 2012)

GBD 2010 health state	Weight (95% uncertainty interval)
Schizophrenia: acute state	0.756 (0.571-0.894)
Spinal cord lesion at neck: untreated	0.676 (0.475-0.837)
Major depressive disorder: severe episode	0.655 (0.469-0.816)
Heroin and other opioid dependence	0.641 (0.459-0.803)
Schizophrenia: residual state	0.576 (0.399-0.756)
Parkinson's disease: severe	0.549 (0.383-0.711)
AIDS cases: not receiving ARV treatment	0.547 (0.328-0.715)
Terminal phase: without medication (for cancers, end-stage kidney/liver disease)	0.519 (0.356-0.683)
Terminal phase: with medication (for cancers, end-stage kidney/liver disease)	0.508 (0.348-0.670)
Rectovaginal fistula	0.492 (0.330-0.660)
Cancer: metastatic	0.484 (0.330-0.643)
Bipolar disorder: manic episode	0.480 (0.323-0.642)
Multiple sclerosis: moderate	0.445 (0.303-0.593)

GBD 2010 health state	Weight (95% uncertainty interval)
Burns of ≥20% total surface area or ≥10% total surface area if head or neck, or hands or wrist involved: long term, without treatment	0.438 (0.298-0.588)
Headache: migraine	0.433 (0.287-0.593)
Motor plus cognitive impairments: severe	0.425 (0.286-0.587)
Acute myocardial infarction: days 1-2	0.422 (0.284-0.566)
Epilepsy: untreated	0.420 (0.279-0.572)
Major depressive disorder: moderate episode	0.406 (0.276-0.551)
Tuberculosis: with HIV infection	0.399 (0.267-0.547)
Fracture of pelvis: short term	0.390 (0.257-0.545)
Alcohol use disorder: moderate	0.388 (0.262-0.529)
Fracture of neck of femur: long term, without treatment	0.388 (0.261-0.532)
COPD and other chronic respiratory problems: severe	0.383 (0.259-0.528)
Cocaine dependence	0.374 (0.235-0.553)
Amphetamine dependence	0.353 (0.215-0.525)
Dementia: moderate	0.346 (0.233-0.475)

GBD 2010 health state	Weight (95% uncertainty interval)
Burns of ≥20% total surface area: short term, with or without treatment	0.333 (0.220-0.472)
Tuberculosis: without HIV infection	0.331 (0.222-0.450)
Cannabis dependence	0.329 (0.223-0.455)
Abdominopelvic problem: severe	0.326 (0.219-0.176)
Stroke: long-term consequences, moderate plus cognition problems	0.312 (0.211-0.433)
Fracture of neck of femur: short term, with or without treatment	0.308 (0.205-0.439)
Cancer: diagnosis and primary therapy	0.294 (0.199-0.411)
Gout: acute	0.293 (0.198-0.404)
Musculoskeletal problems: generalised, moderate	0.292 (0.197-0.410)
Low back pain: acute, without leg pain	0.269 (0.184-0.373)
Parkinson's disease: moderate	0.263 (0.179-0.360)
Crohn's disease or ulcerative colitis	0.255 (0.152-0.314)
Severe traumatic brain injury: short term, with or without treatment	0.235 (0.156-0.331)
HIV cases: symptomatic, pre-AIDS	0.221 (0.146-0.310)
Motor plus cognitive impairments: moderate	0.221 (0.141-0.314)

GBD 2010 health state	Weight (95% uncertainty interval)
Infectious disease: acute episode, severe	0.210 (0.139-0.298)
Diarrhea: moderate	0.202 (0.133-0.299)
Distance vision blindness	0.195 (0.132-0.272)
Decompensated cirrhosis of the liver	0.194 (0.127-0.273)
COPD and other chronic respiratory problems: moderate	0.192 (0.129-0.271)
Disfigurement: level 2, with itch or pain	0.187 (0.125-0.264)
Heart failure, severe	0.186 (0.128-0.261)
Fracture of face bone: short or long term, with or without treatment	0.173 (0.111-0.257)
Musculoskeletal problems: legs, severe	0.171 (0.117-0.240)
Angina pectoris: severe	0.167 (0.109-0.234)
Anaemia: severe	0.164 (0.112-0.228)
Amputation of one leg: long term, without treatment	0.164 (0.111-0.229)
Major depressive disorder: mild episode	0.159 (0.107-0.223)
Fracture of sternum or fracture of one or two ribs: short term, with or without treatment	0.150 (0.098-0.215)
Anxiety disorders: moderate	0.149 (0.101-0.210)

GBD 2010 health state	Weight (95% uncertainty interval)
Crush injury: short or long term, with or without treatment	0.145 (0.093-0.211)
Musculoskeletal problems: arms, moderate	0.144 (0.077-0.159)
Urinary incontinence	0.142 (0.094-0.204)
Injured nerves: long term	0.136 (0.092-0.096)
Fracture of vertebral column: short or long term, with or without treatment	0.132 (0.085-0.195)
Amputation of one arm: long term, with or without treatment	0.130 (0.088-0.185)
Dislocation of knee: long term, with or without treatment	0.129 (0.087-0.178)
Burns of ≥20% total surface area or ≥10% total surface area if head or neck, or hands or wrist involved: long term, with treatment	0.127 (0.086-0.183)
Severe wasting	0.127 (0.081-0.183)
Intellectual disability: severe	0.126 (0.085-0.176)
Abdominopelvic problem: moderate	0.123 (0.083-0.176)
Lymphatic filariasis: symptomatic	0.110 (0.073-0.157)
Diabetic neuropathy	0.099 (0.066-0.145)
Epididymo-orchitis	0.097 (0.063-0.137)

GBD 2010 health state	Weight (95% uncertainty interval)
Burns of <20% total surface area without lower airway burns: short term, with or without treatment	0.096 (0.062-0.140)
Fracture of patella, tibia or fibula, or ankle: short term, with or without treatment	0.087 (0.055-0.127)
Stoma	0.086 (0.055-0.131)
Dislocation of shoulder: long term, with or without treatment	0.080 (0.053-0.116)
Musculoskeletal problems: legs, moderate	0.079 (0.053-0.110)
Injury to eyes: short term	0.079 (0.050-0.118)
Motor impairment: moderate	0.076 (0.050-0.109)
Fracture of skull: short or long term, with or without treatment	0.073 (0.046-0.109)
Severe tooth loss	0.072 (0.048-0.103)
Epilepsy: treated, seizure free	0.072 (0.047-0.106)
Fracture of neck of femur: long term, with treatment	0.072 (0.047-0.105)
Disfigurement: level 2	0.072 (0.006-0.025)
Benign prostatic hypertrophy: symptomatic cases	0.070 (0.046-0.102)
Heart failure: moderate	0.070 (0.044-0.102)

GBD 2010 health state	Weight (95% uncertainty interval)
Angina pectoris: moderate	0.066 (0.043-0.095)
Fracture of radius or ulna: short term, with or without treatment	0.065 (0.040-0.101)
Injured nerves: short term	0.065 (0.040-0.096)
Anaemia: moderate	0.058 (0.038-0.086)
Motor plus cognitive impairments: mild	0.054 (0.033-0.084)
HIV/AIDS cases: receiving ARV treatment	0.053 (0.034-0.079)
Infectious disease: acute episode, moderate	0.053 (0.033-0.081)
Fracture of clavicle, scapula, or humerus: short or long term, with or without treatment	0.053 (0.033-0.080)
Mastectomy	0.038 (0.022-0.059)
Bipolar disorder: residual state	0.035 (0.021-0.055)
Distance vision: moderate impairment	0.033 (0.020-0.052)
Fracture of foot bones: short term, with or without treatment	0.033 (0.019-0.053)
Hearing loss: severe	0.032 (0.018-0.051)
Intellectual disability: mild	0.031 (0.018-0.049)
Hearing loss: profound	0.031 (0.018-0.049)

GBD 2010 health state	Weight (95% uncertainty interval)
Generic uncomplicated disease: worry and daily medication	0.031 (0.017-0.050)
Amputation of finger(s), excluding thumb: long term, with treatment	0.030 (0.018-0.048)
Anxiety disorders: mild	0.030 (0.017-0.048)
Intestinal nematode infections: symptomatic	0.030 (0.016-0.048)
Asthma, partially controlled	0.027 (0.015-0.045)
End-stage renal disease: with kidney transplant	0.027 (0.015-0.043)
Fracture of hand: short term, with or without treatment	0.025 (0.013-0.043)
Hearing loss: moderate	0.023 (0.013-0.038)
Diabetic foot	0.023 (0.012-0.039)
Amputation of one leg: long term, with treatment	0.021 (0.011-0.035)
Impotence	0.019 (0.010-0.034)
Burns of <20% total surface area or <10% total surface area if head or neck, or hands or wrist involved: long term, with or without treatment	0.018 (0.010-0.032)
Ear pain	0.018 (0.009-0.031)
Dislocation of hip: long term, with or without treatment	0.017 (0.008-0.030)

GBD 2010 health state	Weight (95% uncertainty interval)
COPD and other chronic respiratory problems: mild	0.015 (0.007-0.028)
Amputation of thumb: long term	0.013 (0.006-0.025)
Disfigurement: level 1	0.013 (0.006-0.025)
Abdominopelvic problem: mild	0.012 (0.005-0.023)
Dental caries: symptomatic	0.012 (0.005-0.023)
Infertility: primary	0.011 (0.005-0.021)
Periodontitis	0.008(0.003-0.017)
Amputation of toe	0.008 (0.003-0.017)
Infertility: secondary	0.006 (0.002-0.013)
Hearing loss: mild	0.005 (0.002-0.012)
Infectious disease: acute episode, mild	0.005 (0.002-0.011)
Anaemia: mild	0.005 (0.002-0.011)

Appendix 5. Complete List of References for Bone Mineral Density as the Exposure Variable.

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11 SCIENTIFIC PRODUCTION DIRECTLY RELATED TO THE TOPIC OF THIS THESIS

Presentations in International Conferences as first author:

- **Sanchez-Riera L**, Norman R, Veerman L, Vos T, Wilson N, Hoy D, Smith E, March L. Worldwide Quantitative Impact of Low Bone Mineral Density on Hip Fracture Incidence. World congress on osteoporosis, osteoarthritis and musculoskeletal diseases ESCEO-IOF. ***Seville, 2-5 April 2014. Winner of the Lilly scholarship (2500 USD).***
- **Sanchez-Riera L**, Carnahan E, Wilson N, Vos T, Veerman L, Norman R, Lim SS, Hoy D, Smith E, March L. Influence of low bone mineral density on hip fracture incidence in North-Africa Middle East compared to other world regions. Pan Arab Rheumatology Conference. Dubai, 14-17 January 2014.
- (ORAL PRESENTATION) **Sanchez-Riera L**, Norman R, Veerman L, Wilson N, Hoy D, March L. Quantitative Impact of Low Bone Mass on Hip Fracture Incidence in Asia Pacific and Middle East. Asia Pacific League of Associations for Rheumatology Annual Conference, 29 August-1 September 2013. Bali, Indonesia.
- (ORAL PRESENTATION) **Sanchez-Riera L**, Chen C, Wilson N, Hoy D, Smith E, Buchbinder R, Veerman L, Norman R, Vos T, and March L. Selection bias in population-based studies on bone mass. A worldwide perspective. World congress on osteoporosis, osteoarthritis and musculoskeletal diseases ESCEO-IOF. Bordeaux, 21-24 March 2012. ***Winner of the 2012 ESCEO Young Investigator Award (2500 euros).***
- **Sànchez-Riera L**, Wilson N, Chen JS, Kamalaraj N, Macara M, Cok C, Smith E, Santos-Hernandez C, Rodriguez-Portales JA, Zmuda J, Woolf AD, March L.

Global distribution of BMD and T scores in the world. European League Against Rheumatisms Annual Conference. Rome, 16-19 June 2010.

- **Sanchez-Riera L**, Wilson N, Chen JS, Kamalaraj N, Macara M, Cok C, Smith E, Santos-Hernandez C, Rodriguez-Portales JA, Zmuda J, Woolf AD, March L. Quality assessment tool for osteoporosis studies. Asia Pacific League of Associations for Rheumatology Annual Conference. Hong Kong, 11-15 July 2010.
- **Sanchez Riera L**., on behalf of GBD Osteoporosis working Group, Wilson NM., Chen C., Kamalaraj N., Macara M., Kok C., Smith E., Woolf A., Santos C., Rodriguez Portales JA., Zmuda J., Yang L., March L. (2010) Worldwide T scores and risk of hip fracture. International Osteoporosis Foundation (IOF) World Congress on Osteoporosis & 10th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis. Florence, Italy. May 5-8. 2010
- **Sanchez Riera L**., Wilson N., Hoy D., Norman R., Veerman L., Smith E., Woolf A., Vos T., March L., and GBD Musculoskeletal Expert Group (2010) Use of a quality assessment tool for a systematic review on osteoporosis prevalence. International Osteoporosis Foundation (IOF) World Congress on Osteoporosis & 10th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis. Florence, Italy. May 5-8. 2010

EXTENDED REPORT

The global burden attributable to low bone mineral density

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ABSTRACT

Introduction The Global Burden of Disease Study 2010 estimated the worldwide health burden of 291 diseases and injuries and 67 risk factors by calculating disability-adjusted life years (DALYs). Osteoporosis was not considered as a disease, and bone mineral density (BMD) was analysed as a risk factor for fractures, which formed part of the health burden due to falls.

Objectives To calculate (1) the global distribution of BMD, (2) its population attributable fraction (PAF) for fractures and subsequently for falls, and (3) the number of DALYs due to BMD.

Methods A systematic review was performed seeking population-based studies in which BMD was measured by dual-energy X-ray absorptiometry at the femoral neck in people aged 50 years and over. Age- and sex-specific mean ± SD BMD values (g/cm^2) were extracted from eligible studies. Comparative risk assessment methodology was used to calculate PAFs of BMD for fractures. The theoretical minimum risk exposure distribution was estimated as the age- and sex-specific 90th centile from the Third National Health and Nutrition Examination Survey (NHANES III). Relative risks of fractures were obtained from a previous meta-analysis. Hospital data were used to calculate the fraction of the health burden of falls that was due to fractures.

Results Global deaths and DALYs attributable to low BMD increased from 103 000 and 3 125 000 in 1990 to 188 000 and 5 216 000 in 2010, respectively. The percentage of low BMD in the total global burden almost doubled from 1990 (0.12%) to 2010 (0.21%). Around one-third of falls-related deaths were attributable to low BMD.

Conclusions Low BMD is responsible for a growing global health burden, only partially representative of the real burden of osteoporosis.

INTRODUCTION

Osteoporosis is a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of bone fractures.[1] Osteoporotic fractures are defined as those occurring as the result of a low-impact trauma, with consequences ranging from chronic pain to institutionalisation and death.[2–8] For people over 50 years of age living in a developed country, the lifetime risk of sustaining any fracture is ~50% for women and 20% for men.[9] Bone strength primarily reflects the integration of bone mineral density (BMD) and bone quality. The latter is awkward to assess on a population basis, while BMD is a well-defined predictor of fracture risk[10 11] and is easily measurable. For a clinical approach, osteoporosis is defined by a threshold of 2.5 SDs below the mean BMD value of the young reference.[12 13] However, the risk of fracture due to reduced BMD is gradual over a continuum.

This paper follows the comparative risk assessment (CRA) methodology in the Global Burden of Disease (GBD) Study 2010.[14] The two primary outcome measures for the GBD work are deaths and disability-adjusted life years (DALYs), which combine the years lived with disability (YLDs) and the years lost due to premature mortality (years of life lost due to premature mortality (YLLs)).[15] Burden estimates were made for 291 diseases and injuries.[15] The burden arising from 67 risk factors was estimated by determining population attributable fractions (PAFs).[14] Osteoporosis per se was not considered as a disease, and, for the first time, BMD was included in the global burden estimates as a risk factor for fractures, which represented a proportion of the global burden from falls. We summarise the methods used to calculate the contribution of low BMD to the burden of fractures due to falls and present estimates by age and sex by world region. We also document trends in attributable burden between 1990 and 2010. Estimates of burden were limited to populations aged 50 years and older, as osteoporotic fractures represent little burden at younger ages in the general population.

This report is part of the Musculoskeletal Expert Group series within the GBD 2010 Initiative.[14–18] Extended reports on the overall methods,[19] global burden of osteoarthritis,[20] rheumatoid arthritis,[21] gout,[22] low back pain,[23] neck pain,[24] occupationally related low back pain,[25] other musculoskeletal conditions[26] and final conclusions[27] have also been published.

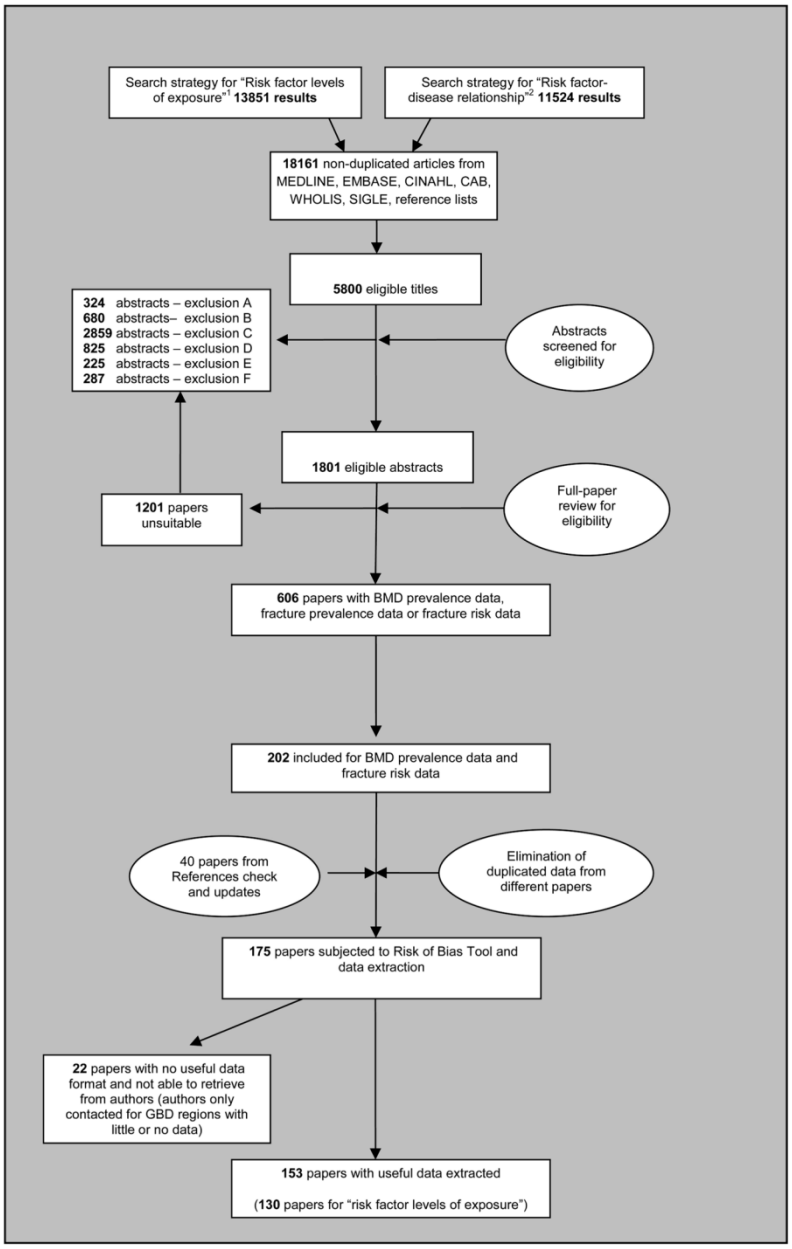
METHODS

Definition of the exposure variable

We performed a systematic review of Medline, Embase, CAB Abstracts, CINAHL, WHOLIS and SIGLE databases for population-based studies published from 1980 to 2010 with BMD values in g/cm^2 measured by dual-energy X-ray absorptiometry (DXA) at the femoral neck (FN). In regions with limited data, we also included other types of study (eg, non-population-based) as long as the sample was considered to be representative of the

Figure 1 Summary for the Systematic Review for Low Bone Mineral Density as a Risk Factor. (A) Flowchart for the systematic review process. Exclusion criteria: A, subsample not representative of the population (ie, athletes); B, non-population-based studies (ie,clinical-based); C, no prevalence/incidence data; D, only subtypes of osteoporosis assessed (ie, steroid-induced osteoporosis); E, sample number <150; F, reviews. Final list of manuscripts used for BMD as the exposure variable can be found in Appendix 1, supplementary online file. (B) Search strategies for the systematic review. Search strategies are shown for BMD as the exposure variable (search strategy 1) and BMD as a risk factor for fractures (search strategy 2). *The whole list of the world countries was used as Subject Headings (SH) in Medline, Embase, CINAHL and CAB abstracts. GBD, global burden of disease; BMD, bone mineral density.

A



B

1. Search strategy for "Risk factor levels of exposure"

(osteoporosis OR osteopenia OR osteopaenia OR bone mineral density OR radiolucency)

AND

(prevalen* OR inciden* OR cross-sectional OR cross sectional OR epidemiol* OR survey OR population-based OR population based OR population study OR population sample OR cohort OR follow-up OR follow up OR longitudinal OR regist* OR data collection)

AND

2. Search strategy for "Risk factor-disease relationship"

(osteoporosis OR osteopenia OR osteopaenia OR bone mineral density OR radiolucency)

AND

(fracture* OR risk)

AND

(GBD Countries SH)*

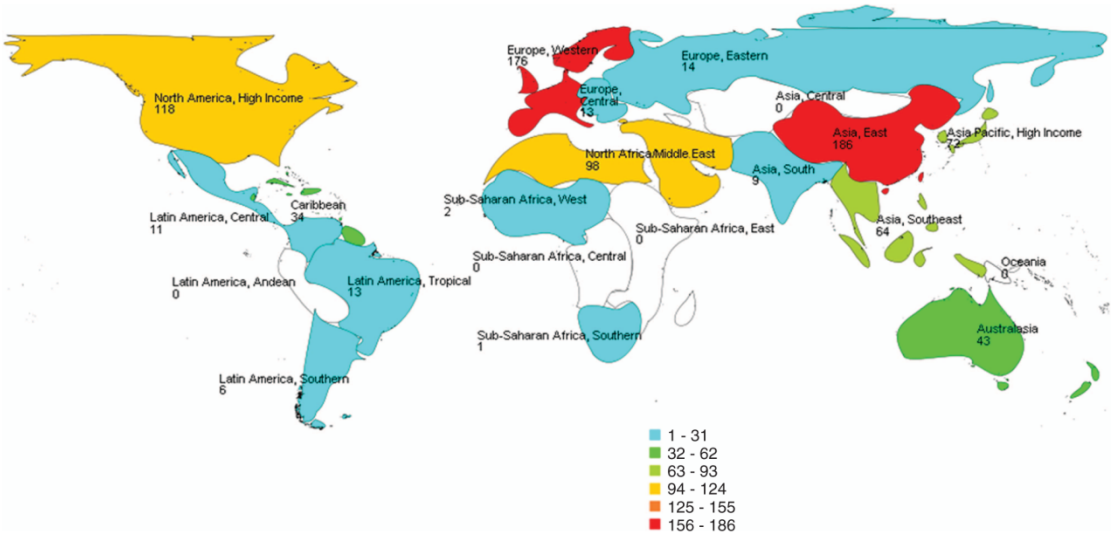


Figure 2 Number of data points of mean bone mineral density at the femoral neck measured by dual-X-ray absorptiometry by each of the 21 GBD world regions. All years (1980–2010), all ages, both sexes. Regions in white have no data. GBD, global burden of disease.

national population. Central DXA is the most validated technique for measuring BMD.[12 13] The location at the FN is justified by the evidence that the morbidity and mortality related to hip fracture (the osteoporotic outcome with the highest burden) is better predicted when BMD is measured at the FN rather than the spine or forearm.[11] Furthermore, measurement at the FN has been found to correlate well with vertebral and other osteoporotic fractures.[11]

Data extraction and processing

A database was developed and implemented in MS Excel, and information was extracted from included studies into the following predetermined fields for the exposure variable: region, country, year of publication, study type, study sample size, population description, coverage, urbanicity (rural, urban or both), start year of data collection, last year of data collection, age group start, age group end, sex, ethnicity, DXA manufacturer, DXA FN-specific coefficient of variation, and mean BMD value in g/cm^2 and SD.

All mean BMD and SD values with different DXA manufacturers (mainly Hologic, Norland and Lunar) were standardised using an international conversion formula[28] to standardise mean BMD (sBMD) and SD (sSD).

Finally, a systematic data-cleaning process was performed to identify double-counted data and inconsistencies in the values.

Search strategies and results of the systematic review for the exposure variable are shown in figures 1A,B and 2, respectively.

Modelling strategy

Eligible articles were assessed for bias using a modified version of a validated Risk of Bias (RoB) tool[29] developed for prevalence studies and adapted for osteoporosis.[30] For selection bias, the risk was considered low when most recruited subjects were included, moderate when only healthy subjects were included, and high when subjects with prior fractures were excluded. The RoB tool was not found to have significant predictive value,[30] and, consequently, all studies after the data-cleaning process were included.

As data were available for only selected country–time periods, the mean sBMD and sSD was estimated separately for all country–time periods using DisMod-MR, a Bayesian meta-regression tool developed specifically for GBD 2010.[17] The model included fixed effects for study-specific covariates, and random effects by GBD super-region, region and country. Study-specific covariates accounted for inconsistencies in the raw data—for example, data that were subnational (rather than nationally representative), or data that were collected in a non-gold-standard way (eg, non-population based). National-level covariates can be used in the model to inform the global and country-level trends, and are not study-specific; lag-distributed income per capita, mean body mass index, and availability of milk based on the Food and Agriculture Organization of the United Nations disappearance data (imports plus local production minus exports) were tested. None of these demonstrated a significant improvement in the predictive ability of the model and were therefore not included.

RELATIVE RISK ASSESSMENT: PAF OF LOW BMD TO FRACTURES

Effect size estimates

The estimates of relative risk (RR) for fractures were based on a meta-analysis of 12 population-based studies from Western Europe, USA, Canada, Japan and Australia published in 2005.[11] This study reported age- and sex-adjusted RRs for hip and non-hip fractures attributable to BMD. Our systematic review process also included searches for longitudinal population-based studies with data on RR of fracture related to FN BMD (figure 1). Data were heterogeneous in terms of BMD location measurement, fracture outcome and study design. Only eight relevant prospective studies[31–38] published since 2005 were found, with RR estimates similar to those published in the previous meta-analysis.[11]

The estimates of the gradient of risk (RR/SD) for BMD Z-scores, based on the combined data for men and women, were obtained from the authors of the meta-analysis.[11] The Z-score was established within each study population separately, which made the RRs dependent on the spread within the study

population. For our purposes this was undesirable, and therefore the 'relative' RR/SD values were converted into 'absolute' RR/0.1 g/cm^2 values (table 1) using a weighted average of the spread in BMD values for the populations that were represented in the meta-analysis, as they were estimated in the DisMod-MR output, and so derived risk estimates for men and women separately by 5-year age group.

Theoretical minimum risk exposure distribution and calculation of PAF

Comparative risk assessment (CRA) methodology[14 39] was used to estimate the proportion of fractures that are attributable to age- and sex-specific levels of BMD analysed as a continuous variable. CRA estimates are based on a counterfactual exposure distribution that would result in the lowest population risk that is theoretically possible, referred to as the theoretical minimum risk exposure distribution (TMRED).[40] The sex- and age-specific 90th percentile from the Third National Health and Nutrition Examination Survey (NHANES III),[41] the most broadly accepted standard international reference,[13] was chosen as the TMRED (table 2). The SD of the TMRED was estimated on the basis of the relationship between means and SDs from a regression of all studies in the final dataset that measured means and SDs of BMD.

Using the exposure distributions and the RR for fracture by BMD level defined above, PAFs were calculated[42] for hip fractures, non-hip vertebra fractures (fractures of vertebra occurring without hip fracture) and non-hip fractures, using the following formula:

$$\mathrm{PAF} = \frac{\int_{x=0}^{m} \mathrm{RR}(x)\mathrm{P}(x)dx - \int_{x=0}^{m} \mathrm{RR}(x)\mathrm{P}'(x)dx}{\int_{x=0}^{m} \mathrm{RR}(x)\mathrm{P}(x)dx}$$

where RR(x) is the RR at exposure level x, P(x) is the population distribution of exposure, P′(x) is the counterfactual distribution of exposure, and m the maximum exposure level.

Table 1 Relative risk (RR) of hip and non-hip fractures for each 0.1 g/cm^2 decrease in bone mineral density (BMD)

	RR/0.1 BMD unit decrease					
	Non-hip fractures			Hip fractures		
Age (years)	Mean	LCI	HCI	Mean	LCI	HCI
Men						
50–54	1.152	1.058	1.254	2.603	2.042	3.319
55–59	1.183	1.104	1.268	2.421	1.978	2.961
60–64	1.215	1.147	1.286	2.282	1.938	2.689
65–69	1.249	1.189	1.311	2.177	1.914	2.478
70–74	1.297	1.238	1.357	2.100	1.897	2.324
75–79	1.338	1.279	1.402	1.921	1.781	2.072
80+	1.371	1.302	1.444	1.730	1.627	1.840
Women						
50–54	1.158	1.061	1.265	2.697	2.096	3.470
55–59	1.201	1.114	1.296	2.629	2.109	3.278
60–64	1.237	1.162	1.317	2.466	2.062	2.951
65–69	1.286	1.216	1.358	2.412	2.084	2.792
70–74	1.342	1.274	1.413	2.315	2.064	2.596
75–79	1.398	1.327	1.475	2.118	1.942	2.311
80+	1.438	1.355	1.526	1.878	1.750	2.016

Values are RR of fracture per each 0.1 unit of BMD decrease. Units of BMD are g/cm^2. Adapted from Johnell *et al*.[11]
LCI, lower 95% CI; HCI, high 95% CI.

Table 2 Theoretical-minimum-risk exposure distribution (TMRED) for men and women aged 50 years and over

Age	Mean sBMD	SD
Women		
50–59	1.00	0.14
60–69	0.92	0.14
70–79	0.84	0.13
80+	0.78	0.13
Men		
50–59	1.09	0.16
60–69	1.06	0.16
70–79	1.02	0.16
80+	0.98	0.16

Values are expressed in g/cm^2 and correspond to the age- and sex-specific 90th centile of the mean BMD from NHANES III[41] after internationally recognised standardisation.[28]
sBMD, standardised bone mineral density.

HEALTH BURDEN OF FRACTURES AS A FRACTION OF FALLS

For attributing deaths to low BMD, the difficulty is that deaths are categorised according to cause of injury (ie, falls), not nature of injury (ie, fracture), and low BMD or osteoporosis is not coded as a cause. Fractures can be found as a consequence of many events such as road accident, assault or natural disasters. For the purposes of this analysis, estimates were restricted to fractures due to falls, where we expected most osteoporotic fractures to be coded. It was necessary to turn to hospital data from Brazil,[43] Canada,[44] Mexico[45] and the USA[46 47] to estimate the fraction of in-hospital deaths from falls that involved hip and vertebra fractures. Those with a mention of concurrent head or internal injury were excluded. Other fracture types were also excluded, as these were considered less likely to lead to death, as supported by an analysis of the Australian mortality database.[48] Among those inpatient deaths where the primary cause for admission was a fall, a large fraction, especially at older ages, involved a hip fracture; only a small proportion of deaths associated with a vertebral fracture were not also associated with a hip fracture (table 3). As this was the only data source used to determine the fraction of deaths from falls due to hip fracture or vertebra fracture, it was necessary to apply these age- and sex-specific proportions to falls to every country.

Disability from falls is estimated by the nature of the associated injury, and therefore the short- and long-term disability was estimated for fractures by site. The RRs for hip fracture

Table 3 Fraction of in-hospital deaths from falls involving hip and vertebra fractures

Sex	Age	Hip fracture (%)	Non-hip vertebra fracture (%)
Women	50–59	61.6	2.6
	60–69	73.2	1
	70–79	79.4	0.6
	80+	82.5	0.5
Men	50–59	46	8
	60–69	67.5	4.6
	70–79	79.8	0.9
	80+	84.2	0.4

Percentages express the fraction of in-hospital deaths from falls that involve hip fractures and non-hip vertebra fractures (deaths from vertebral fractures that occur without hip fracture). Calculated with in-patient hospital data from Brazil,[43] Canada,[44] Mexico[45] and the USA.[46 47]

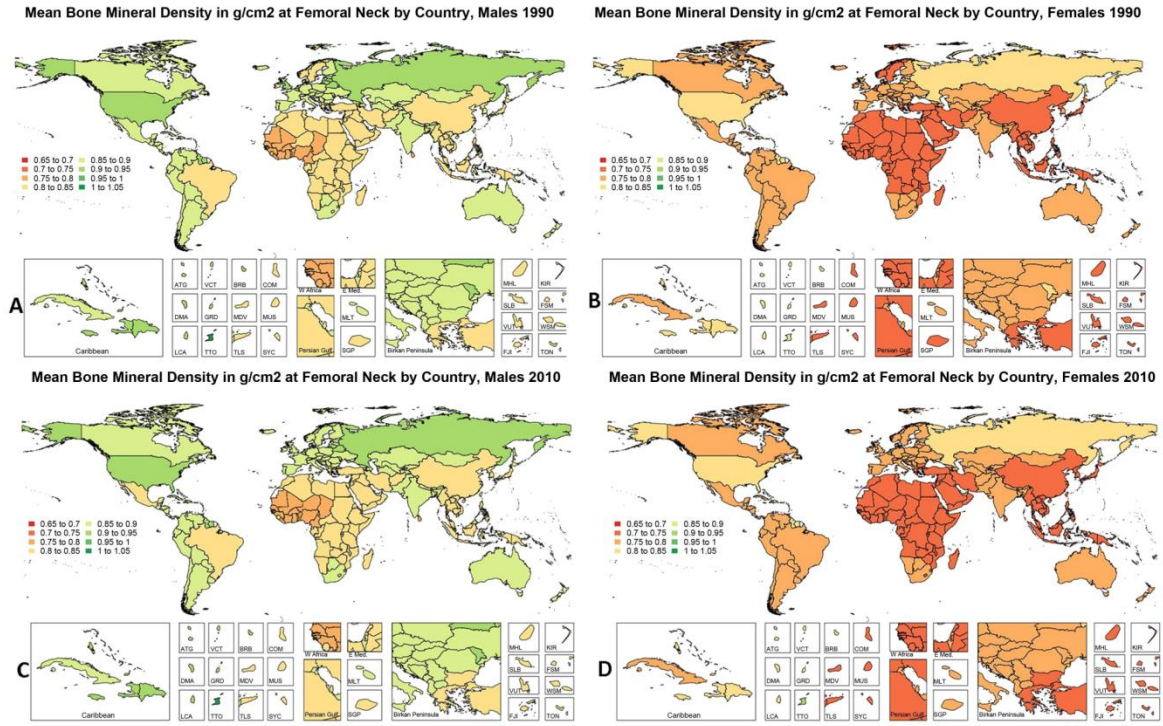


Figure 3 Word distribution of standardised bone mineral density in g/cm^2 at the femoral neck at country level. (A) Men, 1990; (B) women, 1990; (C) men, 2010; (D) women, 2010.

(table 1) were applied to the YLD estimates for hip fracture due to falls sub-cause. The RRs for non-hip fracture (table 1) were applied to YLD estimates for all other fracture sites known to be associated with osteoporosis (clavicle, scapula, humerus, skull, sternum, rib, face bone, radius or ulna, femur, patella, tibia, fibula, ankle, pelvis, vertebral, other extremities). Details on the disability weights for fracture types and methods used to calculate YLDs due to falls can be found elsewhere.[17 18]

RESULTS

There were 130 eligible articles (Appendix 1, supplementary online file), with a total of 860 data points from 49 countries and 17 world regions (figure 2). Worldwide distributions of mean BMD for people aged 50 years and over for 1990 and 2010 are shown in figure 3. Asia and Africa were the world regions with the lowest values of BMD at the FN, while high-income North America, Caribbean and Eastern Europe showed the highest BMD values for both men and women. Although age-adjusted data showed an improving trend for BMD values over time,[49] especially in Asia and Western Europe, BMD at a population level decreased in some regions as a result of the ageing of the population.

For all diseases, injuries and risk factors, data on DALYs, YLDs, YLLs and deaths can be seen online by region, country, year,

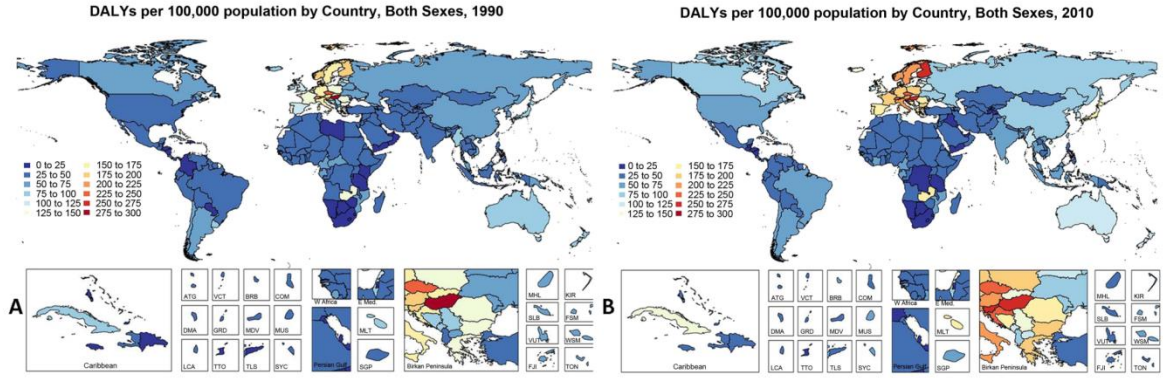


Figure 4 World distribution of disability-adjusted life years (DALYs) for low bone mineral density per 100 000 population at country level. All ages, both sexes. (A) Estimations for 1990; (B) estimations for 2010 (for all estimations for 1990, 2005 and 2010 for men and women at country, region and super-region levels, please visit http://www.healthmetricsandevaluation.org/gbd/visualizations/country).

Table 4 Global burden of low bone mineral density

Year	Sex	Deaths		DALYs		YLLs		YLDs	
		Absolute	Percentage	DALYs	Percentage	Absolute	Percentage	Absolute	Percentage
1990	Both	103 270 (90 672 to 124 230)	0.22 (0.20 to 0.27)	3 125 166 (2 588 901 to 3 811 443)	0.12 (0.10 to 0.15)	1 595 178 (1 411 360 to 1 944 972)	0.08 (0.07 to 0.10)	1 529 989 (1 044 409 to 2 121 696)	0.26 (0.19 to 0.34)
1990	Female	50 455 (40 408 to 62 110)	0.23 (0.19 to 0.29)	1 361 202 (1 101 627 to 1 685 725)	0.12 (0.10 to 0.14)	669 752 (543 744 to 809 200)	0.08 (0.07 to 0.10)	691 450 (468 513 to 989 670)	0.23 (0.16 to 0.31)
1990	Male	52 816 (43 822 to 69 605)	0.21 (0.18 to 0.28)	1 763 964 (1 448 305 to 2 207 969)	0.13 (0.11 to 0.16)	925 426 (771 153 to 1 221 801)	0.09 (0.07 to 0.12)	838 539 (569 103 to 1 184 753)	0.30 (0.22 to 0.39)
2005	Both	168 049 (125 643 to 194 351)	0.33 (0.24 to 0.37)	4 642 366 (3 674 161 to 5 641 433)	0.18 (0.15 to 0.22)	2 526 614 (1 859 581 to 2 932 549)	0.14 (0.10 to 0.16)	2 115 752 (1 446 478 to 2 971 623)	0.29 (0.21 to 0.38)
2005	Female	76 471 (51 059 to 91 865)	0.33 (0.22 to 0.39)	1 923 418 (1 465 495 to 2 382 540)	0.17 (0.13 to 0.21)	978 753 (648 292 to 1 172 601)	0.13 (0.09 to 0.15)	944 665 (637 877 to 1 337 991)	0.25 (0.18 to 0.33)
2005	Male	91 578 (59 947 to 108 685)	0.32 (0.21 to 0.39)	2 718 948 (2 020 242 to 3 341 576)	0.20 (0.15 to 0.24)	1 547 861 (1 016 485 to 1 848 546)	0.15 (0.10 to 0.18)	1 171 086 (794 783 to 1 671 341)	0.33 (0.24 to 0.44)
2010	Both	187 586 (140 636 to 219 906)	0.36 (0.27 to 0.42)	5 216 399 (4 132 978 to 6 418 307)	0.21 (0.17 to 0.25)	2 753 010 (2 031 594 to 3 242 599)	0.16 (0.12 to 0.19)	2 463 388 (1 699 328 to 3 490 237)	0.32 (0.23 to 0.41)
2010	Female	84 146 (57 863 to 102 441)	0.35 (0.25 to 0.43)	2 111 329 (1 627 353 to 2 618 461)	0.19 (0.15 to 0.23)	1 045 989 (725 341 to 1 267 368)	0.15 (0.10 to 0.18)	1 065 340 (719 873 to 1 496 345)	0.26 (0.19 to 0.35)
2010	Male	103 440 (67 743 to 124 596)	0.36 (0.24 to 0.43)	3 105 070 (2 295 173 to 3 830 642)	0.23 (0.17 to 0.28)	1 707 021 (1 089 516 to 2 077 040)	0.17 (0.11 to 0.21)	1 398 048 (961 318 to 1 998 927)	0.37 (0.27 to 0.49)

Values with 95% CI are expressed in absolute values and percentage of all GBD causes.
DALYs, disability-adjusted life years; GBD, global burden of disease; YLDs, years lived with disability; YLLs, years of life lost due to premature mortality.

age and sex (http://www.healthmetricsandevaluation.org/gbd/visualizations/country). Global deaths and DALYs attributable to low BMD increased from 103 000 and 3 125 000 in 1990 to 188 000 and 5 216 000 in 2010, respectively (table 4). The percentage of low BMD in the total global burden almost doubled from 1990 (0.12%) to 2010 (0.21%) (table 4). The fraction of the total regional burden increased in all regions except the Caribbean and Oceania. Asia East and South were the major contributors to the increase in global burden of low BMD. Rates of global DALYs per 100 000 population increased markedly from 1990 to 2010, but the increase was modest after age standardisation (table 5), which reflects population growth and ageing. Rates were higher in Western Europe, Central Europe and high-income Asia Pacific (figure 4 and table 5), while the highest age-standardised rates were more commonly found in developing regions such as Sub-Saharan Africa East and West, Oceania, Asia East and South (table 5).

The PAFs of BMD for falls were generally higher for women than men for both 1990 and 2010. In general, world regions with a low gross domestic product showed the highest PAFs (Asia East and South-East, North Africa-Middle East, Sub-Saharan Africa East and West), with the exception of Eastern Europe. However, big disparities in PAFs were observed among high-income countries, even within the same world region—for example, Scandinavian countries compared with UK (figure 5).

In 1990, global DALYs and deaths attributable to low BMD constituted 12.1% and 29.6% of all falls-related DALYs and deaths, respectively. These percentages increased slightly to 14.8% and 34.7% for 2010 estimates. Table 6 shows percentages of the falls burden due to low BMD by world region.

Low BMD ranked low in terms of attributable DALYs compared with most risk factors, such as dietary factors, high blood pressure, smoking, alcohol use, high fasting plasma glucose, high body mass index, high cholesterol and low physical activity (http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-heatmap). Globally, low BMD ranked 23rd among 25 risk factor categories for 2010 (dietary risk factors clustered into one category and occupational risk factors clustered into one category). By region, the highest ranks for low BMD were observed in Western Europe and high-income Asia Pacific, ranked 12th and 13th, respectively, followed by Central Europe, Australasia and high-income North America at 15th and Asia East at 16th.

DISCUSSION

Although age-adjusted data showed an improving trend of the global BMD values over time, the absolute burden of low BMD increased from 1990 to 2010, probably related to the global growth of the aged population. Higher age-standardised rates of DALYs and higher PAFs in developing regions probably reflect the importance of the potentially modifiable determinants of low BMD (such as nutritional factors and access to healthcare). Low BMD could be responsible for at least one-third of deaths attributable to falls, which is third in the list of major health burdens after road injuries and self-harm, as reported previously.[15] However, the contribution of low BMD to the global health burden compared with other risk factors was low, and it is likely that the burden of osteoporosis has been underestimated for several reasons.

First, the choice of an age- and sex-specific TMRED masked the important role of age and sex in fracture risk,[50] and it may explain in part the lower health burden of BMD compared with other risk factors. Given that the gradient of risk of fracture for each unit of BMD decrease is the same in men and women,[11] the use of the young female reference seems reasonable in clinical settings. In the GBD framework, however, risk factor

Table 5 Rates of DALYs per 100 000 population by GBD region in 1990 and 2010

	1990				2010			
Location	**All ages**		**Age-standardised**		**All ages**		**Age-standardised**	
Asia Pacific, high-income	80.79	(59.46 to 106.37)	65.85	(48.44 to 86.62)	138.31	(102.67 to 181.06)	63.43	(47.48 to 82.93)
Asia, Central	38.02	(26.64 to 50.90)	54.17	(37.79 to 72.72)	37.46	(26.80 to 52.41)	49.41	(35.15 to 69.01)
Asia, East	68.64	(56.02 to 84.10)	94.54	(77.36 to 116.21)	92.00	(72.58 to 113.50)	86.45	(68.28 to 106.73)
Asia, South	44.15	(32.85 to 59.10)	86.92	(65.52 to 115.84)	64.87	(42.01 to 88.54)	102.87	(66.89 to 140.05)
Asia, Southeast	45.39	(35.50 to 55.66)	85.71	(66.39 to 104.44)	62.48	(46.36 to 77.96)	84.81	(62.64 to 105.55)
Australasia	87.20	(60.27 to 124.09)	69.28	(48.18 to 98.00)	117.27	(79.24 to 164.28)	67.52	(44.60 to 94.86)
Caribbean	48.02	(35.73 to 60.13)	66.22	(49.20 to 83.01)	62.56	(46.94 to 79.73)	66.16	(49.74 to 84.60)
Europe, Central	154.51	(121.21 to 192.20)	121.69	(95.48 to 151.15)	187.81	(141.40 to 245.17)	108.44	(82.07 to 142.07)
Europe, Eastern	60.65	(39.77 to 86.20)	45.32	(29.78 to 64.35)	85.59	(54.13 to 118.30)	54.61	(34.90 to 75.23)
Europe, Western	140.64	(108.32 to 181.16)	83.04	(63.72 to 107.39)	183.26	(140.75 to 239.56)	85.86	(65.50 to 112.71)
Latin America, Andean	35.06	(25.74 to 45.51)	67.45	(49.50 to 87.44)	36.57	(27.09 to 48.39)	50.41	(37.37 to 66.73)
Latin America, Central	27.00	(21.75 to 33.29)	51.84	(41.80 to 63.95)	35.65	(28.15 to 43.87)	47.45	(37.43 to 58.41)
Latin America, Southern	63.37	(44.87 to 86.13)	64.96	(45.86 to 88.32)	63.86	(45.05 to 87.23)	50.92	(35.90 to 69.74)
Latin America, Tropical	29.45	(21.24 to 39.82)	52.47	(37.74 to 70.95)	56.82	(37.06 to 75.07)	63.95	(41.54 to 84.41)
North Africa/Middle East	30.78	(23.18 to 40.86)	66.54	(50.20 to 88.00)	37.45	(27.85 to 49.71)	60.63	(45.36 to 80.72)
North America, high-income	43.48	(28.23 to 59.15)	31.57	(20.62 to 42.99)	70.82	(43.07 to 99.00)	41.83	(25.21 to 58.36)
Oceania	56.02	(39.92 to 76.49)	147.40	(106.54 to 199.03)	41.21	(30.75 to 55.27)	91.17	(69.18 to 118.80)
Sub-Saharan Africa, Central	30.92	(23.39 to 39.60)	77.97	(59.17 to 99.77)	27.08	(20.45 to 35.20)	73.34	(55.58 to 95.12)
Sub-Saharan Africa, Eastern	37.20	(29.19 to 48.64)	96.50	(75.27 to 125.60)	42.24	(28.34 to 53.42)	103.90	(69.87 to 131.93)
Sub-Saharan Africa, Southern	15.51	(10.70 to 21.08)	36.91	(25.43 to 50.07)	22.20	(15.40 to 30.10)	38.17	(26.33 to 51.75)
Sub-Saharan Africa, Western	46.15	(37.28 to 56.03)	114.76	(92.56 to 138.91)	44.07	(36.03 to 52.63)	108.31	(87.83 to 130.19)
Global	58.95	(48.83 to 71.89)	77.89	(64.51 to 94.96)	75.71	(59.99 to 93.15)	79.87	(63.28 to 98.22)

Values with 95% CIs are rates of DALYs per 100 000 population. All ages, both sexes. Age standardisation was obtained using the global standard proposed by the WHO in 2001 (http://www.who.int/healthinfo/paper31.pdf).
DALYs, disability-adjusted life years; GBD, global burden of disease.

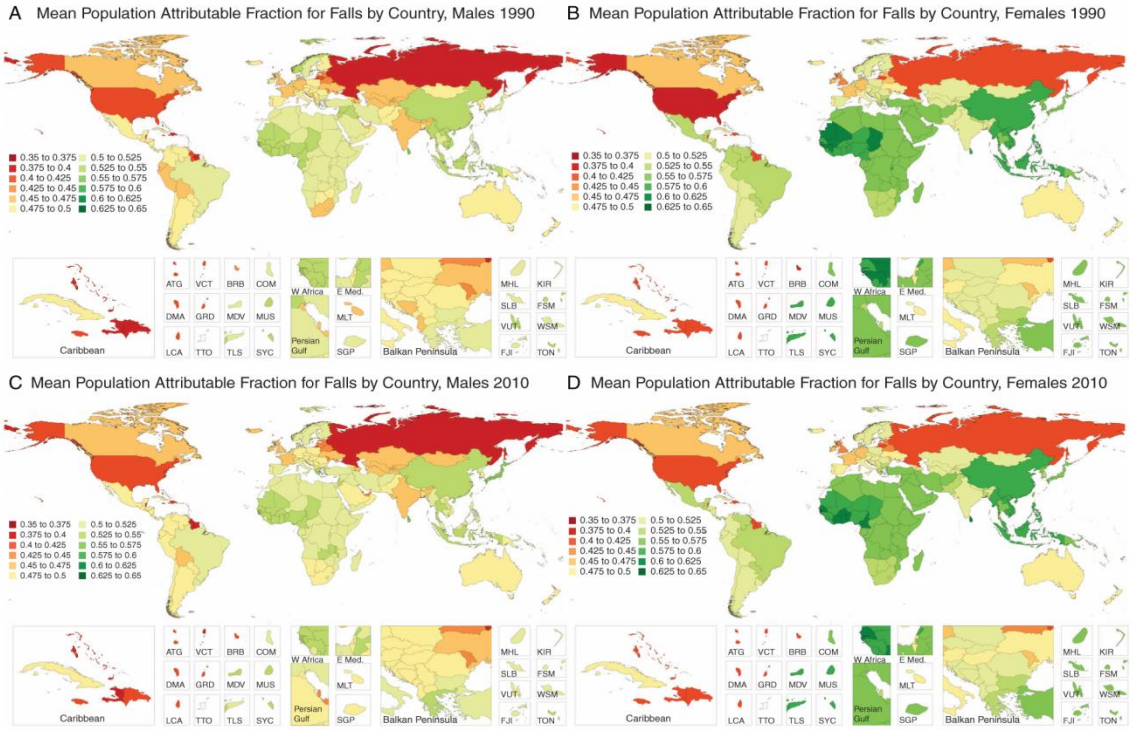


Figure 5 Age-standardized population attributable fraction (PAF) of low bone mineral density for falls. Values are expressed on 0–1 scale. (A) Men, 1990; (B) women, 1990; (C) men, 1990; (D) women, 2010. Age standardization was obtained using the global standard proposed by the WHO in 2001 (http://www.who.int/healthinfo/paper31.pdf).

Table 6 Burden of low bone mineral density as a percentage of falls-related burden by GBD region and year

Region	1990						2010					
	DALYs		YLLs		YLDs	Deaths	DALYs		YLLs		YLDs	Deaths
Asia Pacific, high income	16.3	(13.6 to 19.3)	21.7	(18.8 to 25.8)	14.4	(11.4 to 17.6)	38.0	(33.3 to 42.9)	22.3	(18.8 to 25.8)	38.2	(32.1 to 42.6)	18.1	(14.7 to 21.5)	50.5	(44.3 to 55.6)
Asia, Central	8.0	(6.4 to 9.4)	4.9	(4.1 to 5.6)	9.7	(7.4 to 11.9)	12.7	(10.9 to 14.3)	8.5	(6.9 to 10.1)	6.0	(4.7 to 7.3)	9.7	(7.6 to 11.7)	14.0	(11.6 to 16.3)
Asia, East	13.7	(11.6 to 15.6)	14.6	(11.5 to 16.9)	12.7	(10.4 to 15.0)	32.8	(27.8 to 36.7)	17.5	(15.2 to 20.0)	21.8	(18.6 to 25.7)	14.1	(11.7 to 16.7)	39.7	(35.4 to 44.6)
Asia, South	8.9	(7.0 to 11.0)	9.1	(7.0 to 11.5)	8.7	(6.2 to 11.1)	21.6	(17.5 to 25.8)	11.9	(9.0 to 14.8)	13.7	(10.1 to 17.8)	9.2	(6.7 to 11.7)	28.3	(21.8 to 34.4)
Asia, Southeast	13.8	(11.6 to 16.2)	17.7	(14.0 to 21.6)	10.5	(8.7 to 12.4)	35.3	(30.3 to 40.8)	16.3	(13.6 to 19.1)	23.2	(19.3 to 26.8)	11.3	(9.3 to 13.3)	40.1	(35.1 to 44.9)
Australasia	15.0	(11.1 to 18.7)	27.2	(21.6 to 32.3)	12.7	(9.1 to 16.4)	40.5	(30.5 to 48.2)	17.3	(12.9 to 21.5)	35.2	(27.3 to 41.6)	14.3	(10.3 to 18.2)	44.3	(32.6 to 52.7)
Caribbean	13.6	(10.7 to 16.3)	19.0	(14.7 to 22.9)	9.4	(7.3 to 11.6)	36.8	(28.2 to 43.7)	12.6	(9.7 to 15.3)	24.8	(19.3 to 29.7)	8.3	(6.3 to 10.4)	40.3	(29.5 to 48.4)
Europe, Central	18.9	(16.0 to 21.8)	26.4	(23.2 to 29.4)	14.6	(12.0 to 17.5)	39.9	(34.2 to 44.7)	20.0	(16.9 to 23.2)	32.0	(28.1 to 35.2)	16.0	(13.2 to 19.0)	43.1	(37.1 to 47.8)
Europe, Eastern	11.1	(7.7 to 14.4)	13.8	(9.6 to 17.3)	9.7	(6.4 to 13.0)	24.0	(16.9 to 29.9)	12.7	(8.7 to 16.0)	16.1	(11.0 to 20.2)	10.3	(6.7 to 13.6)	25.9	(17.9 to 32.3)
Europe, Western	18.5	(15.8 to 21.3)	30.9	(27.0 to 34.8)	14.4	(12.1 to 16.6)	40.9	(34.6 to 46.7)	20.1	(17.0 to 23.1)	36.8	(32.5 to 40.6)	16.1	(13.4 to 19.1)	43.7	(37.1 to 48.9)
Latin America, Andean	9.3	(7.4 to 11.2)	9.6	(7.6 to 11.6)	9.1	(6.9 to 11.5)	23.4	(19.2 to 27.3)	11.7	(9.2 to 13.9)	13.4	(10.9 to 15.8)	10.8	(8.0 to 13.5)	30.2	(24.8 to 34.6)
Latin America, Central	11.0	(9.5 to 12.5)	11.4	(10.0 to 13.1)	10.5	(8.4 to 12.6)	27.5	(24.4 to 30.7)	14.7	(12.5 to 16.9)	18.7	(15.5 to 21.2)	11.5	(9.4 to 13.6)	36.1	(31.5 to 40.1)
Latin America, Southern	14.3	(10.9 to 17.5)	20.1	(16.2 to 23.8)	12.1	(8.6 to 15.6)	37.3	(29.8 to 43.1)	15.3	(12.0 to 18.7)	26.2	(21.1 to 30.8)	12.8	(9.8 to 16.0)	42.0	(33.1 to 49.0)
Latin America, Tropical	11.3	(9.1 to 13.6)	11.2	(9.0 to 14.0)	11.4	(8.8 to 14.2)	26.8	(21.8 to 32.1)	17.1	(12.9 to 20.8)	22.6	(15.8 to 27.2)	13.6	(10.3 to 16.8)	40.0	(31.7 to 46.9)
North Africa/Middle East	8.6	(7.3 to 10.0)	5.6	(4.2 to 7.0)	10.5	(8.8 to 12.2)	17.1	(13.6 to 20.7)	10.5	(9.1 to 11.9)	8.9	(7.8 to 10.3)	11.2	(9.4 to 13.1)	23.2	(20.8 to 26.0)
North America, high income	13.5	(9.4 to 17.4)	24.1	(17.3 to 30.2)	8.7	(5.7 to 11.6)	34.9	(23.1 to 43.7)	17.2	(11.4 to 22.7)	31.3	(21.8 to 39.1)	10.5	(7.0 to 13.8)	38.0	(25.0 to 47.1)
Oceania	10.2	(8.1 to 12.5)	9.2	(6.4 to 12.4)	10.8	(8.4 to 13.4)	20.9	(16.1 to 26.2)	10.7	(8.3 to 13.0)	11.6	(7.8 to 15.7)	10.0	(7.7 to 12.1)	24.5	(18.1 to 30.5)
Sub-Saharan Africa, Central	6.9	(4.0 to 12.0)	6.0	(2.6 to 14.3)	9.5	(7.4 to 11.7)	16.2	(8.7 to 30.7)	7.1	(4.6 to 11.0)	6.3	(3.1 to 13.0)	9.3	(7.3 to 11.4)	16.7	(9.9 to 28.7)
Sub-Saharan Africa, East	9.4	(6.2 to 13.1)	9.6	(5.4 to 15.0)	9.4	(7.8 to 11.0)	24.2	(15.9 to 32.0)	12.0	(9.0 to 14.4)	13.1	(8.8 to 16.2)	9.6	(8.0 to 11.4)	29.7	(22.8 to 33.9)
Sub-Saharan Africa, Southern	9.6	(7.2 to 11.8)	14.7	(11.3 to 18.2)	8.0	(5.9 to 10.2)	31.0	(24.5 to 37.1)	10.7	(8.4 to 13.1)	17.6	(13.8 to 21.7)	8.8	(6.5 to 11.0)	34.9	(28.0 to 41.3)
Sub-Saharan Africa, West	5.1	(3.3 to 9.1)	4.1	(2.6 to 8.7)	10.9	(8.9 to 13.0)	13.9	(9.8 to 23.1)	6.7	(5.1 to 9.0)	5.7	(4.1 to 8.4)	10.8	(9.0 to 12.6)	18.3	(14.0 to 23.7)
Global	12.1	(11.1 to 13.2)	12.7	(11.3 to 14.7)	11.5	(10.3 to 12.8)	29.6	(27.4 to 32.0)	14.8	(13.4 to 16.0)	17.3	(15.4 to 19.1)	12.7	(11.4 to 13.9)	34.7	(32.2 to 37.1)

Values with 95% CI represent low bone mineral density burden expressed as the percentage of falls-related burden. All ages, both sexes.
DALYs, disability-adjusted life years; YLDs, years lived with disability; GBD, global burden of disease; YLLs, years of life lost due to premature mortality.

analysis focuses on modifiable risk factors. The TMRED should be possible at the population level and supported by convincing epidemiological evidence of a continuous risk reduction to that exposure distribution.[16] Longitudinal studies[51 52] have demonstrated that a small percentage of older people can maintain their bone mass over time in the absence of risk factors for osteoporosis. However, the extent to which the differences in BMD observed by age and sex are modifiable is not certain. Men have a higher BMD than women, women show faster rates of bone loss after menopause than men,[52–54] and there is no definitive evidence that individuals can maintain their young peak bone mass as they age. There is also a significant genetic component to the ability to retain bone mass.[55 56] On the basis of this evidence, we used a TMRED that was age- and sex-specific. In order to enable worldwide comparisons, an international reference standard is recommended,[57] and the choice of an American reference (NHANES III) might lead to overestimates or underestimates of the risk depending on the world region. However, NHANES III is the reference used in the meta-analysis from which we derived the risk relationship between BMD and fractures.[11] Further research into the modifiability of BMD would help to inform the choice of TMRED.

Separating deaths due to specific fractures from overall deaths due to falls was not straightforward. Osteoporotic fractures are defined as those occurring as the result of a low-impact trauma, but hospital data on falls-related deaths did not include the nature of the injury. Our review did not find prospective population studies with data on mortality due to falls-related fractures covering both sexes and all ages over 50 years. Most of the studies reporting deaths from falls-related fractures were carried out retrospectively from medical charts and death certificates, or they were restricted to frail older populations. This made it difficult to determine what percentage of all falls in a population leads to a fracture-related death.

Hip fracture and clinical vertebral fractures have been shown to be the first and second most important sites, respectively, for osteoporotic fracture-related deaths.[5 58 59] For our mortality analysis, we used in-hospital data, and other fracture types were excluded, as they were less likely to be the underlying cause of death. However, this may have contributed to underestimation of the mortality burden given the evidence that other osteoporotic fracture sites are related to a higher risk of long-term mortality compared with age- and sex-matched peers.[5 60 61] A prospective population-based study conducted over an 18-year period in Australia[5] showed that the fall-fracture event was likely to be missed out as an underlying cause for some deaths that occurred a long time after the fall, particularly in non-hip and non-vertebral fractures. However, long-term mortality after fractures is tedious to interpret within the scope of the GBD Study. Previous studies have demonstrated that mortality is highly related to baseline frailty,[62–65] and it is hard to estimate what percentage of the excess mortality is really due to the fracture event.

As the exposure variable-measuring method, DXA is considerably more expensive and technically more complicated than measurement systems for other risk factors such as hypertension or body mass index. Consequently, the availability of DXA scans is limited,[66] leading to a possible selection bias towards countries with better access to DXA scans. Selecting the FN as the location of the fracture further restricted the number of papers that could be included. Furthermore, the application of standardisation equations among different DXA manufacturers[28] is unlikely to have removed all differences, especially between models from the same manufacturer.[67 68] In addition, BMD has low sensitivity in identifying fracture risk,[69] being purely a quantitative value that does not account for other mechanical properties known to influence bone strength, and consequently leading to an underestimation of the burden associated with osteoporosis.

Another important limitation is selection bias in the source studies. Most of the studies excluded subjects with a history of fracture, bone metabolism diseases, or receiving treatments that might affect bone metabolism. We expected to find discrepancies in the BMD values among different study groups depending on the exclusion or inclusion of such subjects, but linear regression models failed to prove this assumption. The reasons for this are not fully apparent, but it might be related to the heterogeneity among studies. We recommend including patients with previous fractures or a diagnosed bone disease in similar future studies. This is particularly important in elderly populations, as the percentage of individuals with a history of previous fragility fractures is high and excluding such subjects makes the sample not truly representative of the real population and underestimates the real risk.

CONCLUSION

This analysis demonstrates that low BMD is a growing global health burden. However, this is likely to reflect only a small part of the true burden of osteoporosis, given that BMD cannot reflect other important components of bone strength. For future studies of GBD, we strongly recommend a focus on osteoporosis as a disease rather than a risk factor. Health information systems should be better equipped to detect fragility fractures and long-term mortality related to them. The information provided could be used to better inform targeted clinical and public health prevention and management programmes.

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Contributors LSR was the leader for the Osteoporosis Working Group and led the writing of the article. EC, TV, SSL, RN, LV, DH, JMN and LM reviewed the different drafts of the article, sent comments and suggested changes. LSR performed most of the systematic review process and coordinated the extraction data team formed by ES, NW, MM, JSC, YL, NK, JMN, CSH and CK. DH, LSR, TV, LV, RN, JMN and LM developed the Risk of Bias Tool adapted to low bone mineral density as a risk factor in the GBD Study. LSR, LV, RN, EC, TV, LM and SSL developed the estimates of risk-specific exposure, theoretical-minimum-risk exposure distribution, and RR inputs, and checked and interpreted results. TV and SSL were members of the core team for the GBD Study and supervised all the estimates analysis. LM was the MSK Expert Group Leader and led the networking with world experts and supervised the overall work; ES and DH coordinated the Osteoporosis Working Team within the rest of the MSK Expert Group and the GBD Study Group.

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12 SCIENTIFIC PRODUCTION DURING THE THESIS PERIOD RELATED TO THE GBD INITIATIVE AND OTHER EPIDEMIOLOGICAL STUDIES ON MUSCULOSKELETAL DISEASES

All Published Articles

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Reflecting on the global burden of musculoskeletal conditions: lessons learnt from the Global Burden of Disease 2010 Study and the next steps forward.

Hoy DG, Smith E, Cross M, **Sanchez-Riera L**, Blyth FM, Buchbinder R, Woolf AD, Driscoll T, Brooks P, March LM.

The objective of this paper is to provide an overview of the strengths, limitations and lessons learned from estimating the burden from musculoskeletal (MSK) conditions in the Global Burden of Disease 2010 Study (GBD 2010 Study). It should be read in conjunction with the other GBD 2010 Study papers published in this journal. The strengths of the GBD 2010 Study include: the involvement of a MSK expert group; development of new and more valid case definitions, functional health states, and disability weights to better reflect the MSK conditions; the extensive series of systematic reviews undertaken to obtain data to derive the burden estimates; and the use of a new, more advanced version of the disease-modelling software (DisMod-MR). Limitations include: many regions of the world did not have data; the extent of heterogeneity between included studies; and burden does not include broader aspects of life, such as participation and well-being. A number of lessons were learned. Ongoing involvement of experts is critical to ensure the success of future efforts to quantify and monitor this burden. A paradigm shift is urgently needed among global agencies in order to alleviate the rapidly increasing global burden from MSK conditions. Prevention and control of MSK disability are required, along with health system changes. Further research is needed to improve understanding of the

predictors and clinical course across different settings, and the ways in which MSK conditions can be better managed and prevented.

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The Spanish Burden of Disease 2010: Neurological, mental and substance use disorders.

Lara E, Garin N, Ferrari AJ, Tyrovolas S, Olaya B, **Sànchez-Riera L,** Whiteford HA, Haro JM.

INTRODUCTION:

We used data from the Global Burden of Disease, Injuries, and Risk Factors Study 2010 to report on the burden of neuropsychiatric disorders in Spain.

MATERIALS AND METHODS:

The summary measure of burden used in the study was the disability-adjusted life-year (DALY), which sums of the years of life lost due to premature mortality (YLLs) and the years lived with disability (YLDs). DALYs were adjusted for comorbidity and estimated with 95% uncertainty intervals.

RESULTS:

The burden of neuropsychiatric disorders accounted for 18.4% of total all-cause DALYs generated in Spain for 2010. Within this group, the top five leading causes of DALYs were: depressive disorders, Alzheimer's disease, migraine, substance-use disorders, and anxiety disorder, which accounted for 70.9% of all DALYs due to neuropsychiatric disorders. Neurological disorders represented 5.03% of total all cause YLLs, whereas mental and substance-use disorders accounted for 0.8%. Mental and substance-use disorders accounted for 22.4% of total YLDs, with

depression being the most disabling disorder. Neurological disorders represented 8.3% of total YLDs.

CONCLUSIONS:

Neuropsychiatric disorders were one of the leading causes of disability in 2010. This finding contributes to our understanding of the burden of neuropsychiatric disorders in the Spanish population and highlights the importance of prioritising neuropsychiatric disorders in the Spanish public health system.

Best Pract Res Clin Rheumatol. 2014;28(3):353-366.

Burden of disability due to musculoskeletal (MSK) disorders.

March L, Smith EU, Hoy DG, Cross MJ, **Sanchez-Riera L,** Blyth F, Buchbinder R, Vos T, Woolf AD.

This chapter summarises the global and regional prevalence, disability (Years Lived with Disability (YLDs)) and overall burden (Disability Adjusted Life Years (DALYs)) and costs for the common musculoskeletal disorders including low back and neck pain, hip and knee osteoarthritis, rheumatoid arthritis, gout, and a remaining combined group of other MSK conditions. The contribution of the role of pain in disability burden is introduced. Trends over time and predictions of increasing MSK disability with demographic changes are addressed and the particular challenges facing the developing world are highlighted.

BMC Med. 2014:12(1):236.

The burden of disease in Spain: results from the global burden of disease study 2010.

Haro J, Tyrovolas S, Garin N, Diaz-Torne C, Carmona L, **Sanchez Riera L**, Perez-Ruiz F, Murray C.

BACKGROUND.

We herein evaluate the Spanish populations trends in health burden by comparing results of two Global Burden of Diseases, Injuries, and Risk Factors Studies (the GBD studies) performed 20 years apart.

METHODS.

Data is part of the GBD study for 1990 and 2010. We present results for mortality, years of life lost (YLLs), years lived with disability, and disability-adjusted life years (DALYs) for the Spanish population. Uncertainty intervals for all measures have been estimated.

RESULTS .

Non-communicable diseases accounted for 3,703,400 (95% CI 3,648,270-3,766,720) (91.3%) of 4,057,400 total deaths, in the Spanish population. Cardiovascular and circulatory diseases were the main cause of mortality among non-communicable diseases (34.7% of total deaths), followed by neoplasms (27.1% of total deaths). Neoplasms, cardiovascular and circulatory diseases, and chronic respiratory diseases were the top three leading causes for YLLs. The most important causes of DALYs in 2010 were neoplasms, cardiovascular and circulatory diseases, musculoskeletal disorders, and mental and behavioral disorders.

CONCLUSIONS.

Mortality and disability in Spain have become even more linked to non-communicable diseases over the last years, following the worldwide trends. Cardiovascular and circulatory diseases, neoplasms, mental and behavioral disorders, and neurological disorders are the leading causes of mortality and disability. Specific focus is needed from health care providers and policy makers to develop health promotion and health education programs directed towards non-communicable disorders.

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Drug utilization in patients with OA: a population-based study.

Wilson N, **Sanchez-Riera L**, Morros R, Diez-Perez A, Javaid M, Cooper C, Arden N, Prieto-Alhambra D.

OBJECTIVE:

Patients with OA use different drugs in their search for relief. We aimed to study the prevalence of use and combinations of different medications for OA in a population-based cohort of OA patients in Catalonia, Spain, while characterizing users of each of the drugs available, with a particular focus on cardiovascular risk factors.

METHODS:

Data were obtained from the Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) database, which includes electronic medical records and pharmacy invoice data for >5 million people from Catalonia. Study participants were those with a clinical diagnosis of OA in 2006-10. Drugs studied included oral and topical NSAIDs, analgesics (paracetamol, metamizole), opioids (tramadol, fentanyl), cyclooxygenase 2 (COX-2) inhibitors and symptomatic

slow-acting drugs in OA. Drug utilization was described using medication possession ratios (MPRs), equivalent to the proportion of days covered with the drug of interest. The annual incidence of new users in the first year after OA diagnosis from 2006 to 2010 was estimated for all studied drugs among newly diagnosed OA patients using Poisson regression.

RESULTS:

We identified 238 536 study participants. The most common regimen of treatment consisted of at least three drugs (53.9% of patients). The drugs most frequently used regularly (MPR ≥50%) were chondroitin (21.2%), glucosamine (15.8%) and oral NSAIDs (14.4%). The incidence of the use of opioids, COX-2 inhibitors and chondroitin increased over the 5 year period, whereas all others decreased.

CONCLUSION:

Drug combinations are common in the treatment of OA patients, who are thus exposed to potential drug interactions, with unknown impacts on their health. The increasing use of opioids and COX-2 inhibitors is noteworthy because of the potential impact on safety and costs.

Ann Rheum Dis. 2014;73(6):982-9.

The global burden of musculoskeletal conditions for 2010: an overview of methods.

Hoy DG, Smith E, Cross M, **Sanchez-Riera L,** Buchbinder R, Blyth FM, Brooks P, Woolf AD, Osborne RH, Fransen M, Driscoll T, Vos T, Blore JD, Murray C,Johns N, Naghavi M, Carnahan E, March LM.

The objective of this paper is to provide an overview of methods used for estimating the burden from musculoskeletal (MSK) conditions in the Global Burden of Diseases

2010 study. It should be read in conjunction with the disease-specific MSK papers published in Annals of Rheumatic Diseases. Burden estimates (disability-adjusted life years (DALYs)) were made for five specific MSK conditions: hip and/or knee osteoarthritis (OA), low back pain (LBP), rheumatoid arthritis (RA), gout and neck pain, and an 'other MSK conditions' category. For each condition, the main disabling sequelae were identified and disability weights (DW) were derived based on short lay descriptions. Mortality (years of life lost (YLLs)) was estimated for RA and the rest category of 'other MSK', which includes a wide range of conditions such as systemic lupus erythematosus, other autoimmune diseases and osteomyelitis. A series of systematic reviews were conducted to determine the prevalence, incidence, remission, duration and mortality risk of each condition. A Bayesian meta-regression method was used to pool available data and to predict prevalence values for regions with no or scarce data. The DWs were applied to prevalence values for 1990, 2005 and 2010 to derive years lived with disability. These were added to YLLs to quantify overall burden (DALYs) for each condition. To estimate the burden of MSK disease arising from risk factors, population attributable fractions were determined for bone mineral density as a risk factor for fractures, the occupational risk of LBP and elevated body mass index as a risk factor for LBP and OA. Burden of Disease studies provide pivotal guidance for governments when determining health priority areas and allocating resources. Rigorous methods were used to derive the increasing global burden of MSK conditions.

Lancet. 2012 Dec 15;380(9859):2163-96.

Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I,Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C,Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F,Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L,Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B,Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM,Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B,Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F,

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BACKGROUND:

Non-fatal health outcomes from diseases and injuries are a crucial consideration in the promotion and monitoring of individual and population health. The Global Burden of Disease (GBD) studies done in 1990 and 2000 have been the only studies to quantify non-fatal health outcomes across an exhaustive set of disorders at the global and regional level. Neither effort quantified uncertainty in prevalence or years lived with disability (YLDs).

METHODS:

Of the 291 diseases and injuries in the GBD cause list, 289 cause disability. For 1160 sequelae of the 289 diseases and injuries, we undertook a systematic analysis of prevalence, incidence, remission, duration, and excess mortality. Sources included published studies, case notification, population-based cancer registries, other disease registries, antenatal clinic serosurveillance, hospital discharge data, ambulatory care data, household surveys, other surveys, and cohort studies. For most sequelae, we used a Bayesian meta-regression method, DisMod-MR, designed to address key limitations in descriptive epidemiological data, including missing data,

inconsistency, and large methodological variation between data sources. For some disorders, we used natural history models, geospatial models, back-calculation models (models calculating incidence from population mortality rates and case fatality), or registration completeness models (models adjusting for incomplete registration with health-system access and other covariates). Disability weights for 220 unique health states were used to capture the severity of health loss. YLDs by cause at age, sex, country, and year levels were adjusted for comorbidity with simulation methods. We included uncertainty estimates at all stages of the analysis.

FINDINGS:

Global prevalence for all ages combined in 2010 across the 1160 sequelae ranged from fewer than one case per 1 million people to 350,000 cases per 1 million people. Prevalence and severity of health loss were weakly correlated (correlation coefficient -0·37). In 2010, there were 777 million YLDs from all causes, up from 583 million in 1990. The main contributors to global YLDs were mental and behavioural disorders, musculoskeletal disorders, and diabetes or endocrine diseases. The leading specific causes of YLDs were much the same in 2010 as they were in 1990: low back pain, major depressive disorder, iron-deficiency anaemia, neck pain, chronic obstructive pulmonary disease, anxiety disorders, migraine, diabetes, and falls. Age-specific prevalence of YLDs increased with age in all regions and has decreased slightly from 1990 to 2010. Regional patterns of the leading causes of YLDs were more similar compared with years of life lost due to premature mortality. Neglected tropical diseases, HIV/AIDS, tuberculosis, malaria, and anaemia were important causes of YLDs in sub-Saharan Africa.

INTERPRETATION:

Rates of YLDs per 100,000 people have remained largely constant over time but rise steadily with age. Population growth and ageing have increased YLD numbers and crude rates over the past two decades. Prevalences of the most common causes of YLDs, such as mental and behavioural disorders and musculoskeletal disorders, have not decreased. Health systems will need to address the needs of the rising numbers of individuals with a range of disorders that largely cause disability but not mortality. Quantification of the burden of non-fatal health outcomes will be crucial to understand how well health systems are responding to these challenges. Effective and affordable strategies to deal with this rising burden are an urgent priority for health systems in most parts of the world.

Lancet. 2012;380(9859):2224-60.

A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN,Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG,Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL,Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder

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BACKGROUND:

Quantification of the disease burden caused by different risks informs prevention by providing an account of health loss different to that provided by a disease-by-disease

analysis. No complete revision of global disease burden caused by risk factors has been done since a comparative risk assessment in 2000, and no previous analysis has assessed changes in burden attributable to risk factors over time.

METHODS:

We estimated deaths and disability-adjusted life years (DALYs; sum of years lived with disability [YLD] and years of life lost [YLL]) attributable to the independent effects of 67 risk factors and clusters of risk factors for 21 regions in 1990 and 2010. We estimated exposure distributions for each year, region, sex, and age group, and relative risks per unit of exposure by systematically reviewing and synthesising published and unpublished data. We used these estimates, together with estimates of cause-specific deaths and DALYs from the Global Burden of Disease Study 2010, to calculate the burden attributable to each risk factor exposure compared with the theoretical-minimum-risk exposure. We incorporated uncertainty in disease burden, relative risks, and exposures into our estimates of attributable burden.

FINDINGS:

In 2010, the three leading risk factors for global disease burden were high blood pressure (7·0% [95% uncertainty interval 6·2-7·7] of global DALYs), tobacco smoking including second-hand smoke (6·3% [5·5-7·0]), and alcohol use (5·5% [5·0-5·9]). In 1990, the leading risks were childhood underweight (7·9% [6·8-9·4]), household air pollution from solid fuels (HAP; 7·0% [5·6-8·3]), and tobacco smoking including second-hand smoke (6·1% [5·4-6·8]). Dietary risk factors and physical inactivity collectively accounted for 10·0% (95% UI 9·2-10·8) of global DALYs in 2010, with the most prominent dietary risks being diets low in fruits and those high in sodium. Several risks that primarily affect childhood communicable diseases,

including unimproved water and sanitation and childhood micronutrient deficiencies, fell in rank between 1990 and 2010, with unimproved water and sanitation accounting for 0·9% (0·4-1·6) of global DALYs in 2010. However, in most of sub-Saharan Africa childhood underweight, HAP, and non-exclusive and discontinued breastfeeding were the leading risks in 2010, while HAP was the leading risk in south Asia. The leading risk factor in Eastern Europe, most of Latin America, and southern sub-Saharan Africa in 2010 was alcohol use; in most of Asia, North Africa and Middle East, and central Europe it was high blood pressure. Despite declines, tobacco smoking including second-hand smoke remained the leading risk in high-income north America and western Europe. High body-mass index has increased globally and it is the leading risk in Australasia and southern Latin America, and also ranks high in other high-income regions, North Africa and Middle East, and Oceania.

INTERPRETATION:

Worldwide, the contribution of different risk factors to disease burden has changed substantially, with a shift away from risks for communicable diseases in children towards those for non-communicable diseases in adults. These changes are related to the ageing population, decreased mortality among children younger than 5 years, changes in cause-of-death composition, and changes in risk factor exposures. New evidence has led to changes in the magnitude of key risks including unimproved water and sanitation, vitamin A and zinc deficiencies, and ambient particulate matter pollution. The extent to which the epidemiological shift has occurred and what the leading risks currently are varies greatly across regions. In much of sub-Saharan Africa, the leading risks are still those associated with poverty and those that affect children.

Lancet. 2012;380(9859):2197-223.

Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.

Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R,Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F,Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C,Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F,Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L,Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B,Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM,Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F,Gillum RF, Gmel G, Gonzalez-Medina D, Gosselin R, Grainger R, Grant B,

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BACKGROUND:

Measuring disease and injury burden in populations requires a composite metric that captures both premature mortality and the prevalence and severity of ill-health. The 1990 Global Burden of Disease study proposed disability-adjusted life years (DALYs) to measure disease burden. No comprehensive update of disease burden worldwide incorporating a systematic reassessment of disease and injury-specific epidemiology has been done since the 1990 study. We aimed to calculate disease burden worldwide and for 21 regions for 1990, 2005, and 2010 with methods to enable meaningful comparisons over time.

METHODS:

We calculated DALYs as the sum of years of life lost (YLLs) and years lived with disability (YLDs). DALYs were calculated for 291 causes, 20 age groups, both sexes, and for 187 countries, and aggregated to regional and global estimates of disease burden for three points in time with strictly comparable definitions and methods. YLLs were calculated from age-sex-country-time-specific estimates of mortality by cause, with death by standardised lost life expectancy at each age. YLDs were

calculated as prevalence of 1160 disabling sequelae, by age, sex, and cause, and weighted by new disability weights for each health state. Neither YLLs nor YLDs were age-weighted or discounted. Uncertainty around cause-specific DALYs was calculated incorporating uncertainty in levels of all-cause mortality, cause-specific mortality, prevalence, and disability weights.

FINDINGS:

Global DALYs remained stable from 1990 (2·503 billion) to 2010 (2·490 billion). Crude DALYs per 1000 decreased by 23% (472 per 1000 to 361 per 1000). An important shift has occurred in DALY composition with the contribution of deaths and disability among children (younger than 5 years of age) declining from 41% of global DALYs in 1990 to 25% in 2010. YLLs typically account for about half of disease burden in more developed regions (high-income Asia Pacific, western Europe, high-income North America, and Australasia), rising to over 80% of DALYs in sub-Saharan Africa. In 1990, 47% of DALYs worldwide were from communicable, maternal, neonatal, and nutritional disorders, 43% from non-communicable diseases, and 10% from injuries. By 2010, this had shifted to 35%, 54%, and 11%, respectively. Ischaemic heart disease was the leading cause of DALYs worldwide in 2010 (up from fourth rank in 1990, increasing by 29%), followed by lower respiratory infections (top rank in 1990; 44% decline in DALYs), stroke (fifth in 1990; 19% increase), diarrhoeal diseases (second in 1990; 51% decrease), and HIV/AIDS (33rd in 1990; 351% increase). Major depressive disorder increased from 15th to 11th rank (37% increase) and road injury from 12th to 10th rank (34% increase). Substantial heterogeneity exists in rankings of leading causes of disease burden among regions.

INTERPRETATION:

Global disease burden has continued to shift away from communicable to non-communicable diseases and from premature death to years lived with disability. In sub-Saharan Africa, however, many communicable, maternal, neonatal, and nutritional disorders remain the dominant causes of disease burden. The rising burden from mental and behavioural disorders, musculoskeletal disorders, and diabetes will impose new challenges on health systems. Regional heterogeneity highlights the importance of understanding local burden of disease and setting goals and targets for the post-2015 agenda taking such patterns into account. Because of improved definitions, methods, and data, these results for 1990 and 2010 supersede all previously published Global Burden of Disease results.

Lancet. 2012;380(9859):2129-43.

Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010.

Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A,Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Bin Abdulhak A, Blyth F, Bourne R, Braithwaite T, Brooks P, Brugha TS, Bryan-Hancock C,Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Díaz-Torné C,Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, Jarvis D, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez

AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, McGill N, McGrath J, Mensah GA, Meyer AC, Michaud C, Moran A, Mori R,Murdoch ME, Naldi L, Newton CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT,Remuzzi G, Richardson K, Room R, Saha S, Sampson U, **Sanchez-Riera L**, Segui-Gomez M, Shahraz S, Shibuya K, Singh D, Sliwa K, Smith E, Soerjomataram I,Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Taylor HR, Tleyjeh IM, van der Werf MJ, Watson WL, Weatherall DJ, Weintraub R, Weisskopf MG, Whiteford H, Wilkinson JD, Woolf AD, Zheng ZJ, Murray CJ, Jonas JB.

BACKGROUND:

Measurement of the global burden of disease with disability-adjusted life-years (DALYs) requires disability weights that quantify health losses for all non-fatal consequences of disease and injury. There has been extensive debate about a range of conceptual and methodological issues concerning the definition and measurement of these weights. Our primary objective was a comprehensive re-estimation of disability weights for the Global Burden of Disease Study 2010 through a large-scale empirical investigation in which judgments about health losses associated with many causes of disease and injury were elicited from the general public in diverse communities through a new, standardised approach.

METHODS:

We surveyed respondents in two ways: household surveys of adults aged 18 years or older (face-to-face interviews in Bangladesh, Indonesia, Peru, and Tanzania; telephone interviews in the USA) between Oct 28, 2009, and June 23, 2010; and an open-access web-based survey between July 26, 2010, and May 16, 2011. The

surveys used paired comparison questions, in which respondents considered two hypothetical individuals with different, randomly selected health states and indicated which person they regarded as healthier. The web survey added questions about population health equivalence, which compared the overall health benefits of different life-saving or disease-prevention programmes. We analysed paired comparison responses with probit regression analysis on all 220 unique states in the study. We used results from the population health equivalence responses to anchor the results from the paired comparisons on the disability weight scale from 0 (implying no loss of health) to 1 (implying a health loss equivalent to death). Additionally, we compared new disability weights with those used in WHO's most recent update of the Global Burden of Disease Study for 2004.

FINDINGS:

13,902 individuals participated in household surveys and 16,328 in the web survey. Analysis of paired comparison responses indicated a high degree of consistency across surveys: correlations between individual survey results and results from analysis of the pooled dataset were 0·9 or higher in all surveys except in Bangladesh (r=0·75). Most of the 220 disability weights were located on the mild end of the severity scale, with 58 (26%) having weights below 0·05. Five (11%) states had weights below 0·01, such as mild anaemia, mild hearing or vision loss, and secondary infertility. The health states with the highest disability weights were acute schizophrenia (0·76) and severe multiple sclerosis (0·71). We identified a broad pattern of agreement between the old and new weights (r=0·70), particularly in the moderate-to-severe range. However, in the mild range below 0·2, many states had significantly lower weights in our study than previously.

INTERPRETATION:

This study represents the most extensive empirical effort as yet to measure disability weights. By contrast with the popular hypothesis that disability assessments vary widely across samples with different cultural environments, we have reported strong evidence of highly consistent results.

Osteoarthritis Cartilage. 2011;19(2):147-54.

The role of pain and functional impairment in the decision to recommend total joint replacement in hip and knee osteoarthritis: an international cross-sectional study of 1909 patients. Report of the OARSI-OMERACT Task Force on total joint replacement.

Gossec L, Paternotte S, Maillefert JF, Combescure C, Conaghan PG, Davis AM, Gunther KP, Hawker G, Hochberg M, Katz JN, Kloppenburg M, Lim K,Lohmander LS, Mahomed NN, March L, Pavelka K, Punzi L, Roos EM, **Sanchez-Riera L**, Singh JA, Suarez-Almazor ME, Dougados M; OARSI-OMERACT Task Force "total articular replacement as outcome measure in OA".

OBJECTIVE:

To assess the pain and functional disability levels corresponding to an indication for total joint replacement (TJR) in hip and knee osteoarthritis (OA).

METHODS:

DESIGN:

International cross-sectional study in 10 countries.

PATIENTS:

Consecutive outpatients with definite hip or knee OA attending an orthopaedic outpatient clinic. Gold standard measure for recommendation for TJR: Surgeon's decision that TJR is justified.

OUTCOME MEASURES:

Pain (ICOAP: intermittent and constant osteoarthritis pain, 0-100) and functional impairment (HOOS-PS/KOOS-PS: Hip/Knee injury and Osteoarthritis Outcome Score Physical function Short-form, 0-100).

ANALYSES:

Comparison of patients with vs without surgeons' indication for TJR. Receiver Operating Characteristic (ROC) curve analyses and logistic regression were applied to determine cut points of pain and disability defining recommendation for TJR.

RESULTS:

In all, 1909 patients were included (1130 knee/779 hip OA). Mean age was 66.4 [standard deviation (SD) 10.9] years, 58.1% were women; 628/1130 (55.6%) knee OA and 574/779 (73.7%) hip OA patients were recommended for TJR. Although patients recommended for TJR (yes vs no) had worse symptom levels [pain, 55.5 (95% confidence interval 54.2, 56.8) vs. 44.9 (43.2, 46.6), and functional impairment, 59.8 (58.7, 60.9) vs. 50.9 (49.3, 52.4), respectively, both $P<0.0001$], there was substantial overlap in symptom levels between groups, even when adjusting for radiographic joint status. Thus, it was not possible to determine cut points for pain and function defining 'requirement for TJR'.

CONCLUSION:

Although symptom levels were higher in patients recommended for TJR, pain and functional disability alone did not discriminate between those who were and were not considered to need TJR by the orthopaedic surgeon.

Best Pract Res Clin Rheumatol. 2010;24(6):793-810.

Osteoporosis and fragility fractures.

Sànchez-Riera L, Wilson N, Kamalaraj N, Nolla JM, Kok C, Li Y, Macara M, Norman R, Chen JS, Smith EU, Sambrook PN, Hernández CS, Woolf A, March L.

The prevalence of osteoporosis is expected to increase with the ageing of the world's population. This article reviews the epidemiology, risk factors and health burden of osteoporosis. In the Global Burden of Disease (GBD) Study 2005, osteoporosis is studied as a risk factor for fracture by considering the bone-mineral-density (BMD) measurement as the continuous exposure variable. We have performed a systematic review seeking population-based studies with BMD data measured by dual-X-ray absorptiometry (DXA). The femoral neck was selected as the unique location and all values were converted into Hologic(®) to enable inclusion of worldwide data for analysis. Provisional results on mean BMD values for different world regions are shown in age breakdowns for males and females 50 years or over, as well as mean T-scores using the young, white, female reference of National Health and Nutrition Examination Survey (NHANES) III. Results show remarkable geographical differences and a time trend towards improvement of the BMD values in Asian and European populations.